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# CLINICAL PROTOCOL CV006037

A Phase 2a Single Dose Study to Evaluate the Effect of BMS-986141 Added on to Aspirin or Ticagrelor or the Combination, on Thrombus Formation in an Ex Vivo Thrombosis Chamber Model in Patients With Stable Coronary Artery Disease and Healthy Participants

**Short Title:**

A Phase 2a Single Dose Study to Evaluate BMS-986141 Added on to Aspirin or Ticagrelor or the Combination, on Thrombus Formation in a Thrombosis Chamber Model in Patients and Healthy Participants

**Protocol Amendment 02**

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## DOCUMENT HISTORY

| Document | Date of Issue | Summary of Change |
|---|---|---|
| Protocol Amendment 02 | 17-Sep-2021 | Modifications [redacted] to clarify treatment allocation, returning to previous therapy, contraception, stopping rules, and add the exclusion of patients with contraindications to study drugs. |
| Protocol Amendment 01 | 18-Mar-2021 | Changed dose and dose formulation to 4 mg oral tablet. |
| Original Protocol | 05-Jan-2021 | Not applicable |

## OVERALL RATIONALE FOR PROTOCOL AMENDMENT 02:

The purpose of this protocol amendment is to apply changes [redacted] Modifications [redacted] have been applied to clarify treatment allocation, returning to previous therapy, contraception, stopping rules, and add the exclusion of patients with contraindications to study drugs. Clarifications to reflect these revisions were made throughout the protocol amendment to maintain consistency.

This protocol amendment will be implemented after the investigator receives all appropriate agency and Investigational Review Board/Ethics Committee approvals.

Generally, only major additions and deletions are provided in this summary document, and all minor grammatical, formatting, rephrasing, stylistic changes, or clarifications, as well as reorganizational changes, are not included.

The rationale(s) for changes to this Protocol Amendment are provided in the summary of key changes table, as shown below:

| SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02 | | |
|---|---|---|
| **Section Number & Title** | **Description of Change** | **Brief Rationale** |
| Table 2-2: On Treatment Procedural Outline (CV006037) - Treatment Arms 1, 2, and 3<br>Table 2-3: On Treatment Procedural Outline (CV006037) - Treatment Arm 4<br>Section 3.3: Benefit/Risk Assessment<br>Section 7.9: Return to Previous Therapy | Added information for participants who will be returning to previous therapy following the study.<br><br>Added reference to new Section 7.9: return to previous therapy.<br><br>Added section to provide guidance for the return to previous therapy upon completion of study therapy. | [redacted] added guidance for return to previous therapies. |
| Table 2-2: On Treatment Procedural Outline (CV006037) - Treatment Arms 1, 2, and 3<br>Table 2-3: On Treatment Procedural Outline (CV006037) - Treatment Arm 4<br>9.4.1.1: Medical Photography | The term 'rash' has been removed and replaced with 'clinical findings' to allow for photos of any change may be taken. Instruction to determine necessity of photographs is at the discretion of the principle investigator has been added. | To clarify any area affected by any clinical finding that can be captured by medical photography as per discretion by the Principal Investigator. |

| SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02 | | |
|---|---|---|
| **Section Number & Title** | **Description of Change** | **Brief Rationale** |
| Section 5.1: Overall Design | Clarification of treatment allocation has been added. | [redacted] define method for allocation of participants to treatment arms. |
| Section 6.1: Inclusion Criteria | 3)a)xi)2) Revised to further clarify type and duration of contraception for women of child bearing potential. | [redacted] duration of contraception requirements for WOCBP has been modified to align with Appendix 4. |
| Section 6.2: Exclusion Criteria | 2)d) Added criteria for contraindications to any of the study drugs. | [redacted] Exclusion Criteria for all contraindications to aspirin, ticagrelor as well as BMS-986141. |
| Section 6.4.1: Retesting During Screening or Lead-in Period<br>Section 7: Treatment<br>Section 9: Study Assessments and Procedures | Removed reference to participant randomization to clarify study participant allocation. | [redacted] define method for allocation of participants to treatment arms. |
| Section 7.7.1: Prohibited and/or Restricted Treatments | Revised #5 to clarify prohibited drugs within one week prior to study treatment | [redacted] define what concomitant medications are prohibited for the patient and healthy subject populations. |
| Section 7.2: Method of Treatment Assignment | Clarification of treatment allocation has been added with reference to Section 5.1. | [redacted] define method for allocation of participants to treatment arms. |
| Section 8.1.2: Stopping Rules | Stopping rules revised to remove the requirement that the AE be the same.<br>Added sentence to clarify that dosing will not resume if any stopping rules are met.<br>Added sentence to clarify that to restart dosing after any stopping rules are met requires approval of a substantial amendment with justification. | [redacted] to clarify Stopping rule requirements. |
| Section 9.2.1: Time Period and Frequency for Collecting AE and SAE information | Updated the location of reference safety information. | [redacted] Safety Information RSI for Aspirin and Ticagrelor are updated. |
| Appendix 4 | Added sentence to further clarify type and duration of contraception for women of child bearing potential.<br>Less than highly effective contraceptive methods moved to unacceptable methods of contraception. | [redacted] duration of contraception requirements for WOCBP has been modified to align with Section 6.1: inclusion criteria.. |

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# 1 SYNOPSIS

Not applicable.

# 2 SCHEDULE OF ACTIVITIES

Study assessment and procedures for screening are presented in Table 2-1, and on-treatment assessments and procedures are presented in Table 2-2 (Treatment Arms 1, 2, and 3) and Table 2-3 for Treatment Arm 4.

**Table 2-1: Screening Procedural Outline (CV006037)**

| Procedure | Screening Visit (Day -28 to Day -1) | Day -7 to -1 Optional Run-in Period | Notes |
|---|---|---|---|
| **Eligibility Assessments** | | | |
| Informed Consent | X | | A participant is considered enrolled only when a protocol specific informed consent is signed. |
| Inclusion/Exclusion Criteria | X | | |
| Medical History | X | | Include any toxicities or allergy related to previous treatments.<br>Include any COVID-19 history, including vaccinations. |
| **Safety Assessments** | | | |
| Physical Examination | X | | |
| Physical Measurements | X | | Height and weight at screening. Body mass index will be calculated at screening. |
| Vital Signs | X | | Includes body temperature, respiratory rate, and seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes. |
| Electrocardiogram | X | | Electrocardiograms should be recorded after the participant has been supine for at least 5 minutes. |
| Clinical Laboratory Tests | X | | Includes blood and urine samples. See Section 9.4.4. Participants are required to fast for at least 10 hours prior to the collection of specimens for clinical laboratory tests. Results must be reviewed by the investigator prior to admission on Day 1. |
| Serology | X | | Includes hepatitis C antibody, hepatitis B surface antigen, and HIV-1 and -2 antibodies. Results must be reviewed by the investigator prior to admission on Day 1. |
| Urine Drug Test | X | | Includes alcohol. Screening results must be available and reviewed prior to admission on Day 1. |

**Table 2-1: Screening Procedural Outline (CV006037)**

| Procedure | Screening Visit (Day -28 to Day -1) | Day -7 to -1 Optional Run-in Period | Notes |
|---|---|---|---|
| Serum Pregnancy Test | X | | For WOCBP only. See Section 9.4.4. Screening results must be reviewed prior to admission on Day 1. |
| Follicle-Stimulating Hormone | X | | Postmenopausal women only. See Section 9.4.4 and Appendix 4. |
| Prior Medication Use | X | | History of prior medications will be assessed. |
| **Optional Run-in Period** | | | |
| Ticagrelor BID, Aspirin, or Ticagrelor BID/Aspirin Administration | | X | Participants who are not previously taking ticagrelor BID, aspirin, or ticagrelor BID + aspirin will be required to take 1 of the medications for at least 7 days prior to Day 1 to ensure steady state has been attained. This is not required for healthy participants enrolled in Treatment Arm 4. |
| **Adverse Event Reporting** | | | |
| Monitor for Non-Serious Adverse Events | | X | Collected only for participants who participate in the Run-in Period. |
| Monitor for SAEs | X | X | All SAEs must be collected from the date of participant's written consent until 30 days after the last dose of study treatment or participant's participation in the study. |

Abbreviations: BID = twice daily; HIV = human immunodeficiency virus; SAE = serious adverse event; WOCBP = women of childbearing potential

**Table 2-2: On Treatment Procedural Outline (CV006037) - Treatment Arms 1, 2, and 3**

| Procedure | Day 1 (Visit 1) | Day 2 (Visit 2/Clinic Discharge[a]) | Day 8/ Study Discharge | Notes |
|---|---|---|---|---|
| **Check-in Assessments** | | | | |
| Inclusion/Exclusion Criteria | X | | | |
| Medical History | X | | | Interim medical history collected before dosing on Day 1. Include any toxicities or allergy related to previous treatments. |
| Prior Medication Use | X | | | History of prior medications will be assessed before dosing on Day 1. |
| Report to Study Site | X | X | | In the morning on Day 1, participants will report to the study site prior to the baseline chamber run. Participants will be released from the clinic after the Hour 2 chamber run is complete and the PK sample is collected. Participants will return to the study site approximately 1 hour before the final chamber run on Day 2. |
| **Safety Assessments** | | | | |
| Physical Examination | X | X | | If the screening physical examination is performed within 24 hours prior to dosing on Day 1, then a single exam may count as both the screening and predose evaluation.<br>Physical examinations will be performed at check-in (if the screening physical examination is performed more than 24 hours prior to dosing on Day 1) and after the chamber run on Day 2.<br>Standard baseline photographs of any area with clinical findings will be taken. See Section 9.4.1.1 |
| Physical Measurements | X | X | | Weight only at check-in and Day 2. Body mass index will be calculated before dosing on Day 1. |
| Vital Signs | X | X | | See note in screening procedures.<br>Vital signs will be obtained at check-in and prior to and after each chamber assessment on Days 1 and 2. |

**Table 2-2: On Treatment Procedural Outline (CV006037) - Treatment Arms 1, 2, and 3**

| Procedure | Day 1 (Visit 1) | Day 2 (Visit 2/Clinic Discharge[a]) | Day 8/ Study Discharge | Notes |
|---|---|---|---|---|
| Electrocardiogram | X | X | | See note in screening procedures.<br>Electrocardiograms will be collected at check-in, and 2 and 24 hours after BMS-986141 dosing. The 2-hour and 24-hour ECGs should be performed prior to the Badimon Chamber run. |
| Clinical Laboratory Tests | X | X | | See note in screening procedures and Section 9.4.4.<br>Laboratory tests will be collected at check-in, and 2 and 24 hours after BMS-986141 dosing. |
| Urine Drug Test | X | | | See note in screening procedures.<br>Performed at check-in; results must be reviewed before BMS-986141 dosing on Day 1. |
| Pregnancy Test | X | | | Performed at check-in; results must be reviewed prior to BMS-986141 dosing on Day 1. |
| Concomitant Medication Use | X | X | X | |
| Monitor for Non-Serious Adverse Events | X | X | X | |
| Monitor for Serious Adverse Events | X | X | X | See note in screening procedures. |
| Follow-up Telephone Call | | | X | ±2 days. The scheduled follow-up telephone call will include review of the specific follow-up instructions and clinically pertinent re-assessment regarding those recommendations which are being provided to the participant to resume any prior medications, including, but not limited to, specific anti-platelet therapeutics. |
| **PK Assessments** | | | | |
| Serial Blood PK Sampling | X | X | | See Table 9.5-1, Table 9.5-2, and Table 9.5-3. |
| Thrombosis Chamber Procedure | X | X | | See Section 9.8. |

**Table 2-2: On Treatment Procedural Outline (CV006037) - Treatment Arms 1, 2, and 3**

| Procedure | Day 1 (Visit 1) | Day 2 (Visit 2/Clinic Discharge[a]) | Day 8/ Study Discharge | Notes |
|---|---|---|---|---|
| | | | | Each participant will undergo a total of 3 thrombosis chamber procedures. |
| **Biomarker Assessments** | | | | See Section 9.8. |
| [redacted] | X | X | | [redacted] |
| [redacted] | X | | | [redacted] |
| Serum collection for SARS-CoV-2 serology | X | | | See Table 9.8-1.<br>Serum collected to be used for measurements of anti-SARS-CoV-2 serology. |
| **Clinical Drug Supplies** | | | | |
| Ticagrelor BID or Aspirin, or Ticagrelor BID + Aspirin Administration | X | X | | Those sourced by the investigator. |
| BMS-986141 Administration | X | | | Those supplied by BMS. |

[a] Evaluations performed prior to study discharge, or for participants who are prematurely discontinued.

Abbreviations: ADME = absorption, distribution, metabolism, and elimination; BID = twice daily; DNA = deoxyribonucleic acid; PD = pharmacodynamic; PK = pharmacokinetic

**Table 2-3: On Treatment Procedural Outline (CV006037) - Treatment Arm 4**

| Procedure | Day 1 (Visit 1) | Day 2 (Visit 2/Clinic Discharge[a]) | Day 8/ Study Discharge | Notes |
|---|---|---|---|---|
| **Check-in Assessments** | | | | |
| Inclusion/Exclusion Criteria | X | | | |
| Medical History | X | | | Interim medical history collected before dosing on Day 1. Include any toxicities or allergy related to previous treatments. |
| Prior Medication Use | X | | | History of prior medications will be assessed before dosing on Day 1. |
| Report to Study Site | X | X | | In the morning on Day 1, participants will report to the study site prior to the baseline chamber run. Participants will be released from the clinic after the Hour 2 chamber run is complete and the PK sample is collected. Participants will return to the study site approximately 1 hour before the final chamber run on Day 2. |
| **Safety Assessments** | | | | |
| Physical Examination | X | X | | If the screening physical examination is performed within 24 hours prior to dosing on Day 1, then a single exam may count as both the screening and predose evaluation.<br>Physical examinations will be performed at check-in (if the screening physical examination is performed more than 24 hours prior to dosing on Day 1) and after the chamber run on Day 2.<br>Standard baseline photographs of any area with clinical findings will be taken. See Section 9.4.1.1. |
| Physical Measurements | X | X | | Weight only at check-in and Day 2. Body mass index will be calculated before dosing on Day 1. |

**Table 2-3: On Treatment Procedural Outline (CV006037) - Treatment Arm 4**

| Procedure | Day 1 (Visit 1) | Day 2 (Visit 2/Clinic Discharge[a]) | Day 8/ Study Discharge | Notes |
|---|---|---|---|---|
| Vital Signs | X | X | | See note in screening procedures.<br>Vital signs will be collected at check-in and prior to and after each chamber assessment on Days 1 and 2. |
| Electrocardiogram | X | X | | See note in screening procedures.<br>Electrocardiograms will be collected at check-in, and 2 and 24 hours after dosing. The 2-hour and 24-hour ECGs should be performed prior to the Badimon Chamber run. |
| Clinical Laboratory Tests | X | X | | See note in screening procedures and Section 9.4.4.<br>Laboratory tests will be collected at check-in, and 2 and 24 hours after dosing. |
| Urine Drug Test | X | | | See note in screening procedures.<br>Performed at check-in; results must be reviewed before dosing on Day 1. |
| Pregnancy Test | X | | | Performed at check-in; results must be reviewed prior to dosing on Day 1. |
| Concomitant Medication Use | X | X | X | |
| Monitor for Non-Serious Adverse Events | X | X | X | |
| Monitor for Serious Adverse Events | X | X | X | See note in screening procedures. |
| Follow-up Telephone Call | | | X | ±2 days. The scheduled follow-up telephone call will include review of the specific follow-up instructions and clinically pertinent re-assessment regarding those recommendations which are being provided to the participant to |

**Table 2-3: On Treatment Procedural Outline (CV006037) - Treatment Arm 4**

| Procedure | Day 1 (Visit 1) | Day 2 (Visit 2/Clinic Discharge[a]) | Day 8/ Study Discharge | Notes |
|---|---|---|---|---|
| | | | | resume any prior medications, including, but not limited to, specific anti-platelet therapeutics. |
| **PK Assessments** | | | | |
| Serial Blood PK Sampling | X | X | | See Table 9.5-4. |
| Thrombosis Chamber Procedure | X | X | | See Section 9.8.<br>Each participant will undergo a total of 3 thrombosis chamber procedures. |
| **Biomarker Assessments** | | | | See Section 9.8. |
| [redacted] | [redacted] | [redacted] | | [redacted] |
| [redacted] | [redacted] | | | [redacted] |
| Serum collection for SARS-CoV-2 serology | X | | | See Table 9.8-2.<br>Serum collected to be used for measurements of anti-SARS-CoV-2 serology. |
| **Clinical Drug Supplies** | | | | |
| BMS-986141 Administration | X | | | Those supplied by BMS. |

[a] Evaluations performed prior to study discharge, or for participants who are prematurely discontinued.

Abbreviations: ADME = absorption, distribution, metabolism, and elimination; DNA = deoxyribonucleic acid; PD = pharmacodynamic; PK = pharmacokinetic

In the event that multiple procedures are required at a single time point, the electrocardiogram (ECG) and vital signs may be obtained up to 15 minutes earlier, and clinical laboratory samples may be obtained up to 5 minutes earlier than the nominal time point, ensuring the pharmacokinetic (PK) samples, biomarker samples, and Badimon Chamber samples can be collected on time.

# 3 INTRODUCTION

Atherothrombotic diseases such as ischemic stroke, transient ischemic attack (TIA), and acute coronary syndrome represent areas of unmet medical need which would likely benefit from improved therapies. Ischemic stroke represents a particularly high unmet need as attempts to reduce stroke recurrence have often failed to improve the net clinical benefit because improvements in efficacy have only been possible with a concomitant increase in the risk of serious bleeding, including intracranial hemorrhage. Acetylsalicylic acid (ASA) has remained the standard of care for secondary prevention after ischemic stroke and TIA because of its perceived low risk of bleeding. In studies to date, treatment with more intensive antiplatelet therapy have demonstrated a reduction in the risk for TIA and stroke.[1]

Each year stroke occurs in approximately 15 million people worldwide. It is responsible for almost 6 million deaths and an additional 5 million individuals are permanently disabled.[2] In the United States, nearly 800,000 people experience TIA or stroke every year, with approximately 87% of these events being due to cerebral ischemia.[3]

TIA and ischemic stroke share a common atherothrombotic pathophysiology, but prognosis varies depending on severity and cause. Current criteria define a TIA as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction. The 90-day risk of stroke following TIA is as high as 17% with the greatest risk apparent in the first week. Patients at highest risk may be identified through neurological assessment scores (ABCD2), ultrasound, and magnetic resonance imaging.

Acetylsalicylic acid has been shown to have modest efficacy, with a 13% reduction in recurrent stroke (odds ratio 0.87, 95% confidence interval [CI] 0.79, 0.97).[4] Alternative antiplatelet therapies or combinations of therapies to improve upon the efficacy of ASA have been sought for many years. The results of the CHANCE study, which examined the use of dual antiplatelet therapy in Chinese patients after acute TIA and minor stroke, suggested that dual antiplatelet therapy may show clinical benefit without increased bleeding risk, but the applicability of these results to patients in other countries awaits confirmation.[5] It remains clear that improved antiplatelet agents with an improved benefit risk profile are needed to help alleviate this significant unmet medical need.

## 3.1 Study Rationale

The effectiveness of antithrombotic agents on thrombus formation cannot be assessed in healthy participants (ie, participants without an active thrombotic process and thrombus formation) with conventional clinical tools. While such agents may alter biomarker measures of coagulation (eg, international normalized ratio [INR] and activated partial thromboplastin time [aPTT]) or platelet activity (eg, platelet aggregation) in both animals and in healthy participants, early phase studies

are limited in their potential to determine the clinical efficacy of novel antithrombotic compounds.[6,7] Advances in ex vivo thrombosis assays, however, may overcome these limitations and lead to new methods for evaluating antithrombotic agents including strategies for optimized dose and schedule selection.

Several ex-vivo perfusion chamber systems have been developed to investigate the mechanisms of thrombus formation. These systems are not dependent on the presence of active thrombotic disease as thrombus formation is stimulated by exposure of flowing blood to an exogenous thrombogenic substrate under controlled conditions. The most widely employed flow devices are the annular perfusion chamber and the parallel-plate perfusion chamber.[6,7] These systems have been successfully used to evaluate the effects of marketed antithrombotic drugs on thrombus formation in vitro and ex vivo in human participants, including differential effectiveness in high (arterial) and low (venous) shear environments dependent thrombus formation.[7,8,9,10,11,12]

This study will be performed using a Badimon perfusion chamber under well controlled rheologic conditions that simulate patent arteries (low shear rate, approximately 212 $s^{-1}$) and stenosed arteries (high shear rate, approximately 1690 $s^{-1}$). This perfusion chamber allows for the evaluation of thrombus formed on carefully prepared strips of porcine aorta (from which the intima and a thin layer of media had been removed) thrombogenic surface exposed to blood flowing directly from the participant's antecubital vein through the perfusion chamber. This experimental thrombosis model allows assessment of thrombus formation by morphometry. Antithrombotic effects can be quantified by the amount (in this case, reduction) of thrombus formed on the exposed substrate.

The primary objective of this study is to assess the effect of BMS-986141 on thrombus formation in an ex-vivo porcine aortic thrombosis chamber model. Key secondary objectives are to assess the safety and tolerability of BMS-986141 when given with aspirin, ticagrelor, or with aspirin and ticagrelor in participants with coronary artery disease; to assess the safety of aspirin alone, ticagrelor alone, and the combination of aspirin and ticagrelor in participants with coronary artery disease; and to assess the safety and tolerability of a single dose of BMS-986141 in normal healthy participants.

## 3.2 Background

BMS-986141 is a novel, highly selective, potent, and orally active antagonist of protease-activated receptor 4 (PAR4). PAR4 is a G-protein coupled receptor present on human platelets.[13] It is activated by thrombin, a key enzyme in the coagulation cascade. Evidence suggests that PAR4 plays a role in the later stages of platelet activation,[14,15,16,17] which is thought to be more important for propagation of thrombus growth and arterial occlusion and less important for hemostasis.[18,19] Consistent with this hypothesis, a cynomolgus monkey model was utilized to demonstrate that BMS-986141 significantly inhibited occlusive thrombus formation with almost no impact on hemostasis. This large window between antithrombic efficacy and bleeding safety suggests that BMS-986141 has potential as a novel therapeutic agent for the treatment of atherothrombotic diseases such as acute TIA and minor stroke.

A detailed description of the pharmacology, toxicology, metabolism, and safety of BMS-986141 is provided in the Investigator's Brochure (IB).[20]

### 3.2.1 Nonclinical Pharmacology and Pharmacokinetics

With an equilibrium binding constant of 0.102 nM for human PAR4, BMS-986141 inhibited PAR4 agonist peptide (AP)-induced cellular calcium mobilization with a concentration at which 50% inhibition observed (IC50) value of 0.45 nM. BMS-986141 is selective for PAR4 because it was ineffective at blocking calcium mobilization stimulated by selective activation of either human protease-activated receptor-1 (PAR1) or human protease-activated receptor-2 (PAR2). In addition, BMS-986141 showed no inhibitory activity when tested against a panel of purified proteases that included thrombin as well as other major coagulation enzymes.

BMS-986141 demonstrated potent, selective, and reversible inhibition of platelet aggregation in vitro and ex vivo.[21] When gamma-thrombin, a selective PAR4 activator, was utilized to stimulate aggregation in human platelet-rich plasma, aggregation was completely inhibited by BMS-986141 with an IC50 value of 2.1 nM. When alpha-thrombin, a dual PAR1 and PAR4 activator, was utilized to stimulate aggregation in washed platelets, BMS-986141 showed significant but partial inhibition of aggregation (up to 76%), suggesting that inhibition of PAR4 can diminish platelet aggregation even in the presence of PAR1 activation. In a whole blood aggregation assay, BMS-986141 inhibited aggregation stimulated by a selective PAR4-AP. BMS-986141 was ineffective at preventing platelet aggregation when blood was stimulated with non-PAR4 platelet activators including adenosine diphosphate (ADP), collagen, PAR1-AP, and a thromboxane A2 mimetic.

Absolute oral bioavailability (F) of BMS-986141 given as a spray-dried dispersion suspension formulation was 25% to 36% in rats, dogs, and monkeys. When BMS-986141 was dosed as a solution or crystalline suspension in rats, F was 74% and 3.6%, respectively, indicating that the F of BMS-986141 is formulation-dependent.[22] BMS-986141 and its major metabolite, BMT-162856, were not substrates for efflux transport in the Caco-2 cell model.[23,24] The apparent elimination half-life (T-HALF) of BMS-986141 was 3.7, 12.8, and 74.7 hours in rats, dogs, and monkeys, respectively, and total plasma clearance was 8.5 mL/min/kg to 14.3 mL/min/kg. The corresponding blood clearance rates were equivalent to $\leq$ 28% of the respective reported liver blood flows.

The volume of distribution at steady state (Vss) in rats, dogs, and monkeys was greater than the respective species' reported plasma volumes, indicative of extravascular distribution. BMS-986141 and its metabolite BMT-162856 were $\geq$ 99.4% bound to serum proteins in humans and nonclinical species; BMS-986141 was not distributed preferentially into either plasma or blood cells.[22,23,24]

In vitro PK drug-drug interaction evaluations showed minimal potential for BMS-986141 to act as a perpetrator for cytochrome P450 (CYP) 3A4 inhibition or induction at clinically relevant dose range (eg, up to 20 mg of BMS-986141). Additional details can be found in the IB.[20]

### 3.2.2 Nonclinical Toxicity

There were no adverse findings in 28-day preclinical toxicology studies. In 3-month studies, the major preclinical findings of note were microscopic changes in the kidneys of some of the monkeys that received the highest dose of BMS-986141, 75 mg/kg/day. These changes have been characterized as moderate degeneration and regeneration of tubular epithelium, and the effect was not observed 1 month after cessation of dosing. There is no evidence of fetal toxicity/teratogenicity in expanded range-finding studies in pregnant rats and rabbits. No cardiovascular safety issues were identified.

Single oral doses of BMS-986141 up to 75 mg/kg were well tolerated in monkeys (maximum observed concentration [Cmax] ≤ 2.66 µg/mL; area under the concentration-time curve from time zero to 24 hours after dose [AUC(0-24)] ≤ 31.9 µg•h/mL), with no BMS-986141 related effects at any dose.

Repeat-dose toxicity studies were conducted at once daily oral doses ranging from 5 mg/kg/day to 150 mg/kg/day in rats and mice, and from 5 mg/kg/day to 75 mg/kg/day in monkeys.

Area under the concentration-time curve [AUC] exposures were dose proportional up to 25 mg/kg/day and less than dose proportional at higher doses in all species, with no sex differences observed in mean AUC values. The major metabolite, BMT-162856, was profiled in the 3-month toxicity studies in rats and monkeys as well as the 2-week mouse toxicokinetic/tolerability study. Exposure to the metabolite was 0.5× to 2.5× that of BMS-986141. Exposures (AUC and Cmax) at the end of the study in the 1-month rat and 3-month monkey toxicity studies were approximately 70% less than those measured after the first dose. The cause for this decreased exposure is unknown, but it is not likely due to increased metabolism based on the lack of effect on liver weights or pathology, similar decrease in systemic exposures (AUC and Cmax) to the metabolite BMT-162856, and no evidence of increased hepatic gene expression of a panel of enzymes (CYP2B1, CYP3A23/3, CYP4A2, enoyl-CoA hydratase/3-hydroxyacyl CoA dehydrogenase, or pyruvate dehydrogenase kinase 4) in rats.[25]

### 3.2.3 Clinical Pharmacology and Safety

Pharmacokinetic data shows that BMS-986141 was rapidly absorbed following single or multiple doses, with time of maximum observed concentration (Tmax) ranging from 1 hours to 4 hours and the terminal T-HALF of approximately 22 hours. Following multiple administration of BMS-986141 (daily doses of 0.3, 2, 10, and 30 mg) for 14 days, there was a slight accumulation of area under the concentration-time curve over the dosing interval (AUC[TAU]) for BMS-986141. The accumulation indexes for AUC(TAU) were less than 2 (ranged from 1.3 to 1.9 across different doses). Both Cmax and AUC of BMS-986141 increased in an approximately dose-proportional manner up to a single dose of 150 mg and multiple doses of 30 mg.

Pharmacodynamics (PD) of BMS-986141 are assessed by ex vivo PAR4-AP-induced platelet aggregation. PD data demonstrated dose- and concentration-dependent inhibition of PAR4-AP-induced platelet aggregation in an almost dichotomous appearance, with the on-set/off-set of inhibition occurring approximately at mean BMS-986141 concentration of 0.5 and 1.5 ng/mL for PAR4-AP concentrations of 12.5 and 25 µM, respectively. This result is

consistent with preclinical findings indicating competitive interaction between BMS-986141 and PAR4-AP.

BMS-986141 has a safe and well tolerated profile in over 100 healthy volunteers across 5 Phase 1 studies using a wide dose range in both single and multiple doses (across 14 days).

## 3.3 Benefit/Risk Assessment

Participants will receive no known health benefit from participating in the study beyond that of an assessment of their overall health status.

BMS-986141 is a highly selective antagonist of PAR4, a thrombin-activated receptor found on human platelets. In animals, BMS-986141 has shown to block thrombosis with minimal increased in bleeding, even when combined with aspirin.[26]

BMS-986141 has a safe and well tolerated profile in over 100 healthy volunteers across 5 Phase 1 studies using a wide dose range in single and multiple doses. The clinical pharmacology profile complements the mechanism of action and optimizes the benefit/risk ratio compared to other antiplatelet agents that have some disadvantages (eg, irreversible, pro-drug).

The impact of BMS-986141 influencing the exposures of ticagrelor or aspirin (and its major metabolite salicylic acid), is based on the nonclinical evaluation of drug interaction potential as a perpetrator. Exposures of BMS-986141 are expected to stay within the range of exposures that have been found to be safe in the single and multiple dose studies. The doses of ticagrelor and aspirin used in this study have been used in other drug-drug interaction studies and have an acceptable safety profile.

BMS-986141 is not expected to have an impact on the PD (platelet aggregation) of ticagrelor, aspirin, or its major metabolite, salicylic acid based on the mechanism of action, preclinical data of PAR4 antagonists, and data from the Phase 1 studies.

There is a small risk of increased bleeding in the dual therapy and triple therapy treatment arms; however, based on accumulated data of previous studies, no major bleeding events using BMS-986141 alone have been observed. Participants who do not currently receive any antiplatelet therapy, or who are currently on aspirin alone as their standard of care, will be excluded from Treatment Arm 3 (triple therapy).

Risks from the phlebotomy and perfusion chamber procedures are standard and include infection, bleeding, bruising, blood clot formation, discomfort at the phlebotomy site, and fainting.

Selected participants, who are currently taking clopidogrel, will be switched to ticagrelor for study purposes. Ticagrelor has been shown to be a more potent antiplatelet agent and to provide better antithrombotic protection in selected patient populations with minimal effects on bleeding liabilities compared to clopidogrel. Guidance for return to previous therapies is provided in Section 7.9.

Ticagrelor and aspirin are both marketed drugs and have substantial clinical use, both individually and in combination. These marketed drugs may prolong bleeding time and increase the risk of bleeding events such as gastrointestinal bleeding. An increased bleeding risk with dual antiplatelet

therapy in patients has been observed but is most relevant to high-risk patients with vascular disease and to longer periods of treatment.

The most commonly reported adverse effects associated with the administration of ticagrelor include dizziness, nausea, shortness of breath, chest pain, irregular heartbeat, rash, and swelling of the face, throat, tongue, lips, and eyes.

The most commonly reported adverse effects associated with the administration of aspirin include dizziness, nausea, vomiting, diarrhea, dyspepsia, heartburn, elevated bilirubin, elevated liver function laboratory tests (liver transaminase, blood urea nitrogen, and creatinine), skin rash, and tinnitus.

If the efficacy and safety profile of PAR4 antagonists in nonclinical studies can be confirmed in humans, BMS-986141 could represent an important advancement in the treatment and prevention of arterial thrombotic disorders.

# 4 OBJECTIVES AND ENDPOINTS

**Table 4-1: Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To assess the effect of BMS-986141 alone and as add on to ticagrelor, aspirin, or the ticagrelor + aspirin combination, on thrombus formation in an ex vivo porcine aortic thrombosis chamber model as compared to pretreatment | • Change from baseline in thrombus area (post-treatment with BMS-986141 versus pretreatment) |
| **Secondary** | |
| • To assess the safety and tolerability of single doses of BMS-986141 when dosed with ticagrelor, aspirin, or the ticagrelor + aspirin combination | • AEs, clinical laboratory values, vital signs, ECGs, or other safety biomarkers |
| • To assess the safety and tolerability of ticagrelor, aspirin, or the ticagrelor + aspirin combination in participants with coronary artery disease | • AEs, clinical laboratory values, vital signs, ECGs, or other safety biomarkers |
| • To assess the safety and tolerability of a single dose of BMS-986141 in normal healthy participants | • AEs, clinical laboratory values, vital signs, ECGs, or other safety biomarkers |
| [redacted] | |
| [redacted] | [redacted] |

**Table 4-1: Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| [redacted] | [redacted] |

# 5 STUDY DESIGN

## 5.1 Overall Design

This is an open-label, single-center, 4-arm study to assess the effect of BMS-986141 on thrombus formation in an ex vivo porcine aortic thrombosis chamber model as compared to pretreatment with BMS-986141. Participants will be screened to determine eligibility within 28 days prior to study treatment.

An optional Run-in Period will take place after screening if participants are taking a similar antiplatelet drug (eg, clopidogrel), a lower dose of ticagrelor twice daily (BID), aspirin, or ticagrelor BID + aspirin or are not currently taking ticagrelor BID, aspirin, or ticagrelor BID + aspirin as part of their standard of care. Participants will receive ticagrelor BID, aspirin, or ticagrelor BID + aspirin daily for at least 7 days under the supervision of the investigator prior to Day 1. The timing of each dose and number of tablets taken will be recorded in a diary. Diaries will be reviewed by study site personnel on Day 1. Participants who do not have 100% compliance will not continue in the study. Participants who do not currently receive any antiplatelet therapy, or who are currently on aspirin alone as their standard of care, will be excluded from Treatment Arm 3 (triple therapy).

Approximately 15 participants each with a confirmed history of (must have at least 1 of the following conditions) proven coronary artery disease (greater than 50% stenosis of proximal coronary artery), prior coronary revascularisation (percutaneous coronary intervention or coronary artery bypass grafting), and/or prior myocardial infarction will be enrolled to 1 of 3 treatment arms

(15 participants per arm, based on their background therapy). Treatment arms will not be randomized but instead be allocated as open-label at the discretion of the Principal Investigator as shown below. Enrollment will require that Treatment Arms 1-3 shall enroll 15 participants each while Treatment Arm 4 (healthy volunteers) will enroll 10 participants.

- Treatment Arm 1: Single oral dose of 90 mg ticagrelor alone, followed by a single oral dose of 4 mg BMS-986141 approximately 2 hours later (Day 1). A second dose of ticagrelor will be taken approximately 12 hours after the first dose. Twice daily dosing of ticagrelor will be continued on Day 2.
- Treatment Arm 2: Single oral dose of 75 mg aspirin alone, followed by a single oral dose of 4 mg BMS-986141 approximately 2 hours later (Day 1). Daily dosing of aspirin will continue on Day 2.
- Treatment Arm 3: Single oral dose of 90 mg ticagrelor + 75 mg aspirin, followed by a single oral dose of 4 mg BMS-986141 approximately 2 hours later (Day 1). A second dose of ticagrelor will be taken approximately 12 hours after the first dose. Ticagrelor + aspirin dosing will continue on Day 2.

Approximately 10 normal healthy participants will be enrolled in Treatment Arm 4 and receive a single dose of 4 mg BMS-986141 on Day 1.

Participants will report to the clinical facility in the morning on Day 1 (Visit 1) prior to BMS-986141 dosing and will return to the clinical facility on Day 2 (Visit 2) approximately 1 hour prior to the final chamber run. Thrombus formation will be determined using the Badimon thrombosis chamber, according to the standard site procedures. Briefly, each participant will have blood drawn from a vein through a cannula set attached to extension tubing. The tubing will be connected to a series of 3 perfusion chambers containing denuded porcine aorta as a thrombogenic surface. A pump placed distal to the chambers will maintain a unidirectional flow at a rate of 10 mL/min. The rheologic conditions in the first chamber will be at a low shear rate (approximately 212 $s^{-1}$) simulating patent arterial flow. The shear rate on the second and third chambers will be high (approximately 1690 $s^{-1}$), simulating stenosed arteries. Each perfusion study will last for 5 minutes. The size of the thrombus formed on the denuded porcine aorta will be assessed by morphometrical analysis. A total of 3 perfusion runs will be performed per participant in each treatment arm.

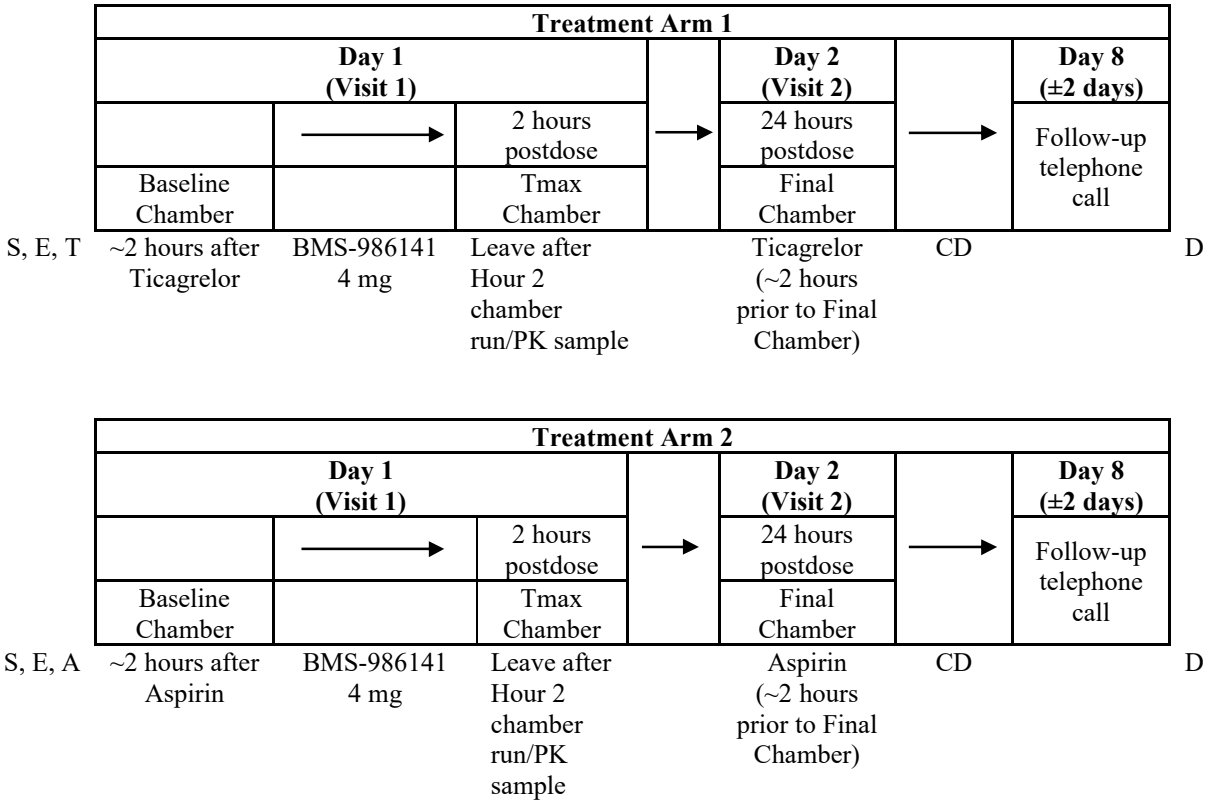
For Treatment Arms 1, 2, and 3, a baseline chamber run will be performed on Day 1 approximately 2 hours after background therapy (ticagrelor, aspirin, or ticagrelor + aspirin) and prior to BMS-986141 administration. A second chamber run will be performed 2 hours following oral administration of BMS-986141. This second chamber run is designed to be conducted at the predicted Tmax of BMS-986141. Participants will be released from the clinic after the Hour 2 chamber run is complete and the Hour 2 PK sample is collected. Participants will return to the clinic on Day 2 approximately 1 hour before the final chamber run. Participants will receive background therapy before the final chamber run, and the final chamber run will be performed on Day 2, approximately 24 hours after BMS-986141 dosing. Participants will be discharged from

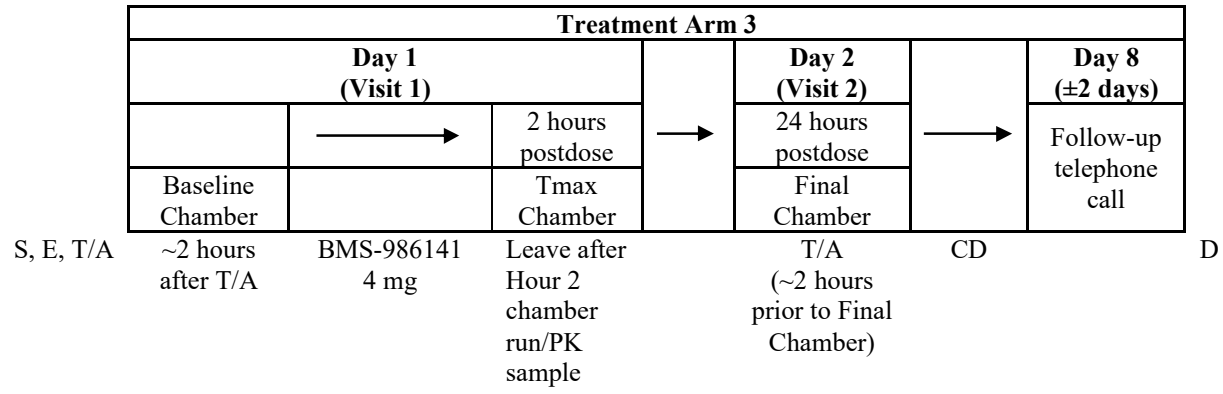
the clinic after the conclusion of this chamber run, with final discharge from the study following telephone follow-up on Day 8 (±2 days).

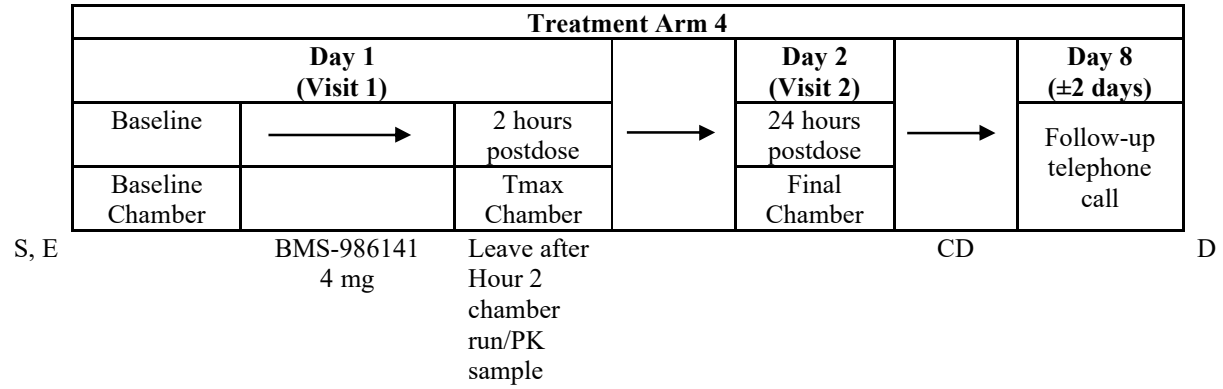
For Treatment Arm 4, a baseline chamber run will be performed on Day 1 prior to BMS-986141 administration. A second chamber run will be performed 2 hours following oral administration of BMS-986141. This second chamber run is designed to be conducted at the predicted Tmax of BMS-986141. Participants will be released from the clinic after the Hour 2 chamber run is complete and the Hour 2 PK sample is collected. Participants will return to the clinic on Day 2 approximately 1 hour before the final chamber run. The final chamber run will be performed approximately 24 hours after dosing. Participants may be discharged from the clinic after the conclusion of this chamber run, with final discharge from the study following telephone follow-up on Day 8 (±2 days).

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

**Figure 5.1-1: Study Design Schematic**






Abbreviations: A = aspirin; CD = clinic discharge; D = study discharge; E = enrollment; PK = pharmacokinetic; S = screening; T = ticagrelor; T/A = ticagrelor + aspirin; Tmax = time of maximum observed concentration

Physical examinations, vital sign measurements, 12-lead ECGs, and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. Participants will be closely monitored for adverse events (AEs) throughout the study. Blood samples will be collected for up to 24 hours after study drug administration for PK and biomarker analysis. Less than 380 mL of blood will be drawn from each participant during the study.

### *5.1.1 Data Monitoring Committee and Other External Committees*

Not applicable.

## 5.2 Number of Participants

Approximately 55 participants (15 participants each in Treatment Arms 1, 2, and 3 and 10 participants in Treatment Arm 4) are planned to be dosed. Sample size determination is discussed in Section 10.1.

## 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 the last 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 and an 8-day treatment period.

## 5.4 Scientific Rationale for Study Design

To characterize the ability of BMS-986141 at a dose of 4 mg to reduce thrombus formation in an ex vivo porcine aortic thrombosis chamber model as compared to ticagrelor BID, aspirin, or ticagrelor BID + aspirin for participants with coronary artery disease. To characterize the ability of BMS-986141 at a dose of 4 mg to reduce thrombus formation in an ex vivo porcine aortic thrombosis chamber model in healthy participants.

## 5.5 Justification for Dose

Single doses of BMS-986141 have been evaluated up to 150 mg and multiple doses up to 30 mg once daily for up to 14 days in study CV006003 with acceptable safety and tolerability. BMS-986141 has also been dosed 20 mg once daily for 14 days in the presence of 325 mg aspirin. No appreciable changes in PK, PD, or bleeding time were observed in the presence of aspirin. The PK were found to be dose proportional in the explored range. BMS-986141 is characterized by rapid absorption with maximal concentrations at 1 to 4 hours postdose and a terminal half-life of about 40 hours. Evaluation of exposures after daily dosing indicates an accumulation index of up to 1.9 and an effective half-life of about 22 hours, suggestive that once daily dosing would be suitable. Integration of mechanistic, cyno-electrically-mediated carotid arterial thrombosis (ECAT) concentration-response data with PK/PD platelet aggregation utilizing 12.5, 25, 50 and 100 uM AP suggest that concentrations of BMS-986141 need to exceed certain thresholds to maintain efficacious inhibition of platelets. Thus, dose selection utilizes steady state trough concentrations as an efficacy target. Upon dosing 4 mg of BMS-986141, two Badimon chamber runs are planned. One at Tmax, which maximize the percentage of participants exceeding the ECAT drug concentration that gives 80% of Emax (EC80), and the second 24 hours after dosing which will maximize the percentage of participants exceeding the ECAT concentration for 50% efficacy (EC50). This evaluation will allow for an assessment of thrombus size reduction at each ECAT target to support dose selection optimization under various background therapies including aspirin monotherapy, ticagrelor monotherapy, and dual antiplatelet therapy (aspirin + ticagrelor).

# 6 STUDY POPULATION

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

## 6.1 Inclusion Criteria

**1) Signed Written Informed Consent**

a) Signed written informed consent must be obtained from the participants in accordance with the requirements of the study center's Independent Ethics Committee (IEC) before initiation of any protocol-required procedures.

**2) Type of Participant and Target Disease Characteristics**

a) Body mass index (BMI) 18.0 to 35.0 kg/$m^2$, inclusive, with a body weight between 50 kg and 120 kg, inclusive. BMI = weight (kg)/(height [m])$^2$ for participants.

b) For Treatment Arms 1, 2, and 3, participant has a history of or has been diagnosed with at least 1 of the following:

i) Prior angiographically proven coronary artery disease (greater than 50% stenosis of proximal coronary artery)

ii) Prior coronary revascularisation (percutaneous coronary intervention or coronary artery bypass grafting)

iii) Prior myocardial infarction

c) For Treatment Arms 1, 2, and 3, participant is eligible as determined by no deviation from normal considered significant by the investigator in medical history, physical examination, 12-lead ECG measurements, and clinical laboratory determinations, except for the cardiovascular history.

d) For Treatment Arm 4, participant is healthy as determined by no deviation from normal considered significant by the investigator in medical history, physical examination, 12-lead ECG measurements, and clinical laboratory determinations.

**3) Age and Reproductive Status**

Investigators shall counsel women of childbearing potential (WOCBP) participants, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy.

- The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Local laws and regulations may require the use of alternative and/or additional contraception methods.

a) Female Participants

i) Females, ages 18 to 75 years, inclusive.

ii) Women who are not of childbearing potential are exempt from contraceptive requirements.

iii) Women participants must have documented proof that they are not of childbearing potential.

iv) WOCBP must have a negative highly sensitive serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study treatment.

v) Additional requirements for pregnancy testing during and after study intervention are located in Section 2, Schedule of Assessments.

vi) The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

vii) WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below and included in the informed consent form.

viii) WOCBP are permitted to use hormonal contraception methods (as described in Appendix 4).

ix) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

(1) Is not a WOCBP

OR

(2) Is a WOCBP and using one of the highly effective contraceptive methods as described in Appendix 4 for the duration of treatment with study drugs (BMS-986141, aspirin, ticagrelor) plus at least 5 half-lives of BMS-986141 (9 days, 5 half-lives of aspirin and ticagrelor are shorter than 9 days)

b) Male Participants

i) Males, ages 18 to 75 years, inclusive.

ii) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below.

iii) Azoospermic males are exempt from contraceptive requirements.

iv) No additional contraceptive measures are required to be used.

## 6.2 Exclusion Criteria

**1) Medical Conditions - All Participants**

a) Women who are breastfeeding

b) Acute coronary syndrome or coronary revascularisation within 3 months of study treatment administration

c) Coagulation disorders (including any abnormal bleeding or blood dyscrasias), anaemia, or renal or hepatic insufficiency

d) Current or recent bleeding, including, but not limited to, epistaxis, gastrointestinal, or urogenital bleeding

e) Acute illness, including a common cold, within 7 days of study treatment administration or any other significant acute or chronic medical illness

f) Active malignancy (excluding localized skin cancer)

g) Current or recent (within 3 months of study drug administration) gastrointestinal disease that could impact upon the absorption of study treatment

h) Any gastrointestinal surgery that could impact upon the absorption of study treatment

i) Any major or traumatic surgery within 12 weeks of screening

j) Donation of blood to a blood bank or in a clinical study (except a screening visit) within 4 weeks of study treatment administration (within 2 weeks for plasma only)

k) Blood transfusion within 4 weeks of study treatment administration

l) Inability to tolerate oral medication

m) Inability to be venipunctured and/or tolerate venous access

n) Recent (within 5 years of study treatment administration) drug or alcohol abuse as defined in Diagnostic and Statistical Manual of Mental Disorders (4th Edition), Diagnostic Criteria for Drug and Alcohol Abuse (Appendix 5)

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

p) Evidence of active coronavirus disease (COVID-19) infection

**2) Medical Conditions - Treatment Arms 1, 2, and 3**

a) Participant does not take 7 consecutive days of ticagrelor BID, aspirin, or ticagrelor BID + aspirin prior to Day 1

b) Participants who do not currently receive any antiplatelet therapy, or who are currently on aspirin alone as their standard of care, will be excluded from Treatment Arm 3 (triple therapy)

c) Current or recent uncontrolled hypertension

d) Participants must not have contraindications to any of the study drugs, specifically to aspirin or ticagrelor, including, but not limited to history of intracerebral hemorrhage

**3) Prior/Concomitant Therapy**

a) Inability to comply with restrictions and prohibited treatments as listed in Section 7.7 Concomitant Therapy

**4) Physical and Laboratory Test Findings**

a) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG, or clinical laboratory determinations beyond what is consistent with the target population (participants with coronary artery disease or healthy participants)

b) Hematocrit < 35%, hemoglobin < 11 g/dL, or platelet count < lower limit of normal

c) Participants at screening or prior to first dose of study treatment with the following abnormal laboratory values, confirmed by repeat

i) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5× upper limit of normal (ULN) for participants in Treatment Arms 1, 2, and 3

ii) ALT or AST > ULN for participants in Treatment Arm 4

iii) Total bilirubin > ULN (participants with mild unconjugated hyperbilirubinemia due to Gilbert's syndrome are excluded)

iv) Creatine kinase > 3× ULN

v) aPTT or prothrombin time/INR > ULN

vi) Blood urea nitrogen or creatinine > ULN

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

i) PR ≥ 210 msec

ii) QRS ≥ 120 msec

iii) QT ≥ 500 msec

iv) QT corrected for heart rate using the Fridericia formula (QTcF) ≥ 450 msec

e) Positive urine screen for drugs of abuse

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

**5) Allergies and Adverse Drug Reaction**

a) History of allergy to aspirin, ticagrelor, BMS-986141, or related compounds

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

**6) Other Exclusion Criteria**

a) Prisoners or participants who are involuntarily incarcerated. (Note: Under specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included as a participant. Strict conditions apply and Bristol-Myers Squibb [BMS] approval is required.)

b) Employee of the investigator or clinical site, or BMS or PPD, with direct involvement in the proposed experiment or other experiments under the direction of that investigator or clinical site, as well as family members of the employees or the investigator

c) Inability to comply with restrictions as listed in Section 6.3 Lifestyle Restrictions

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*

- Participants are not permitted to consume grapefruit-containing products from 3 days prior to the first dose of study treatment until study discharge.
- Participants are not permitted to consume broccoli, cauliflower, radishes, turnips, melons (excluding watermelon), and raw or uncooked red meat from 3 days prior to the first dose of study treatment until clinic discharge.
- Participants should not consume more than 350 mg of Vitamin C from 3 days prior to first dose of study treatment until clinic discharge.
- Participants may not drink water 1 hour before and 1 hour after dosing on Day 1, except as required for dosing. Water may be consumed ad libitum at other times.
- Standard meals will be served by the clinical site. There are no specific restrictions regarding the content of meals and snacks.

### *6.3.2 Caffeine, Alcohol and Tobacco*

- Participants are not permitted to consume alcohol-containing beverages from 3 days prior to first dose of study treatment until clinic discharge.
- Participants are not permitted to consume caffeine-containing products from 3 days prior to first dose of study treatment until clinic discharge.
- Participants are not permitted to smoke or use other nicotine- or tobacco-containing products while at the study site.

### 6.3.3 Activity

Participants are to refrain from strenuous exercise, contact sports, and sunbathing from at least 1 day prior to the first dose until clinic discharge.

## 6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently entered in the study/included in the analysis population. 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, as applicable, 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 that has discontinued the study as a pretreatment failure (ie, participant 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 study allocation 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 2-11, 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 allocation.

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

- BMS-986141 oral tablets at a dose of 4 mg (IP)
- Ticagrelor oral tablets at a dose of 90 mg BID (IP)
- Aspirin oral tablets at a dose of 75 mg (IP)

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.

The study treatments for this study are presented in Table 7-1. Instructions for storage and administration will be provided to the investigative site separate from the protocol.

The investigator will source, purchase, and provide sufficient marketed product of ticagrelor 90-mg tablets and aspirin 75-mg tablets.

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 CV006037**

| Product Description / Class and Dosage Form | Potency | IP/Non-IMP | Blinded or Open Label | Packaging / Appearance | Storage Conditions (per label) |
|---|---|---|---|---|---|
| BMS-986141 tablets | 4 mg | IP | Open label | Tablets in HDPE containers | Refer to labeled instructions |
| Ticagrelor[a] | 90 mg | IP | Open label | Tablets in commercial packaging | Refer to SmPC |
| Aspirin[a] | 75 mg | IP | Open label | Tablets in commercial packaging | Refer to SmPC |

[a] Ticagrelor and aspirin will be sourced by the study investigator and not provided by BMS as local commercial product. Storage should be in accordance with the package insert or summary of product characteristics (SmPC).

Abbreviations: HDPE = high-density polyethylene; IP = investigational product; SmPC = summary of product characteristics

## 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/Dosage level | Dosage formulation Frequency of Administration | Route of Administration |
|---|---|---|---|---|
| **Treatment Arm 1** | | | | |
| A | Ticagrelor[a] | 90 mg | Twice daily dose on Day 1<br>Single dose in the morning of Day 2 | Oral |
| B | BMS-986141 | 4 mg | Single dose on Day 1 | Oral |
| **Treatment Arm 2** | | | | |
| C | Aspirin | 75 mg | Single dose on Day 1 and Day 2 | Oral |
| D | BMS-986141 | 4 mg | Single dose on Day 1 | Oral |
| **Treatment Arm 3** | | | | |
| E | Ticagrelor[a] | 90 mg | Twice daily dose on Day 1<br>Single dose in the morning of Day 2 | Oral |
| | Aspirin | 75 mg | Single dose on Day 1 and Day 2 | Oral |
| F | BMS-986141 | 4 mg | Single dose on Day 1 | Oral |
| **Treatment Arm 4** | | | | |
| G | BMS-986141 | 4 mg | Single dose on Day 1 | Oral |

[a] The second dose of ticagrelor will be administered approximately 12 hours after the first dose.

In the morning on Day 1 and/or Day 2, each participant will receive a single oral dose of the treatment(s) based on their assigned treatment arm. At the time of dosing, water will be administered to the participant along with his/her dose of study drug. The dose will be administered with a total volume of approximately 240 mL of water. 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

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

Treatment arms will not be randomized but instead be allocated as open-label at the discretion of the Principal Investigator as detailed in Section 5.1.

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 dosed.

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. 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 treatment as the participant being replaced, but a new participant number will be assigned to him or her. For example, participant 00004 would be replaced by Participant 00104.

## 7.3 Blinding

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

Aortic strip analysis will be performed blinded. Aortic strips will be assigned and stored with a unique sample number unrelated to the participant number. Aortic strips will be processed by the histology department, who are blinded to the study entirely, and analyzed at a later date by an operator blinded to the aortic strip linked sample numbers.

## 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 investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study participants. The investigational product 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).

For study drugs not provided by BMS and obtained commercially by the site, storage should be in accordance with the product label.

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 / Biocomparability*

Not applicable.

## 7.6 Treatment Compliance

Participants may take part in an optional Run-in Period after screening if participants are taking a similar antiplatelet drug (eg, clopidogrel), a lower dose of ticagrelor BID, aspirin, or ticagrelor BID + aspirin or are not currently taking ticagrelor BID, aspirin, or ticagrelor BID + aspirin as part of their standard of care. Participants will receive ticagrelor BID, aspirin, or ticagrelor BID + aspirin daily for at least 7 days under the supervision of the investigator prior to Day 1. Participants will record the timing of each dose and number of tablets taken in a diary. Diaries will be reviewed by study site personnel on Day 1. Participants who do not have 100% compliance will not continue in the study.

Study drug will be administered in the clinical facility. After administration of study treatments, an examination of the oral cavity is required to verify that a participant has swallowed the oral solution or tablet. The participant should drink the entire aliquot of water given to swallow the oral solution or tablet.

The examiner should have the participant open the mouth and stick out the tongue far enough to permit visualization of the posterior most part of the tongue. A light source should be used to ensure complete visualization, and in some cases, it may be necessary to use a tongue blade. The participant should be directed to move the tongue up and then from side to side. It may be necessary to use a tongue blade to move the tongue far enough to permit full visualization of the area under the tongue. The tongue blade should then be used to inspect the sulcus between the gums and the inner cheeks in all 4 quadrants. The participant should then be asked to lift the upper and lower lips to permit visualization of the sulcus between the inner lip and the gums.

## 7.7 Concomitant Therapy

### *7.7.1 Prohibited and/or Restricted Treatments*

Prohibited and/or restricted medications taken prior to study drug administration in the study are described below. Medications taken within 4 weeks prior to BMS-986141 administration must be recorded on the case report form (CRF). Any SARS-CoV-2 vaccination should be recorded.

1) Prior exposure to BMS-986141.
2) Exposure to any IP or placebo within 4 weeks of study treatment administration.
3) Exposure to any biologics within 5× T-HALF of study treatment administration.
4) Exposure to any vaccines within 7 days of study treatment administration. If participants are receiving the SARS-CoV-2 vaccine as a 2-dose series, the entire series should be completed before enrollment.
5) Use of any other drugs, including over-the-counter medications and herbal preparations, within 1 week prior to study treatment administration.
6) Use of any known strong CYP3A4 inhibitors within 2 weeks prior to study treatment administration or during the study (Appendix 6).

7) Use of anticoagulant therapy within 1 week of screening.
8) Use of any agent, nonsteroidal anti-inflammatory compounds, anticoagulants, fish oil capsules, and gingko, which are known to increase the potential for bleeding within 2 weeks prior to study treatment administration.
9) Use of St John's Wort within 4 weeks prior to study treatment administration and during the study.
10) For participants in Treatment Arm 4, use of dual antiplatelet therapy within 2 weeks of screening.

Participants in Treatment Arms 1, 2, and 3 may receive treatment with medications necessary for maintaining the clinical status of their condition as described in Inclusion Criteria. Background therapy may determine eligibility and treatment arm.

No concomitant medications (prescription, over-the-counter, or herbal) are to be administered during study unless they are prescribed for treatment of specific clinical events. All medications should be approved by the PPD Medical Monitor and BMS Clinical Monitor prior to administration unless it is an emergent situation. Any concomitant therapies must be recorded on the CRF.

### 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.

### 7.9 Return to Previous Therapy

Participants in Treatment Arms 1-3 upon completion of the study, may then resume their prior anti-platelet therapeutics such as aspirin, ticagrelor or clopidogrel, as per recommendations of the Principal Investigator, according to Good Clinical Practice, and consistent with current standard of care.

A follow-up telephone call from the site to each participant shall be conducted to ensure clarity on participant resumption of any prior medications, including prior anti-platelet therapeutics, and to ensure participant safety.

## 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 and only in countries where local regulations permit, 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 the protocol
- Discretion of the investigator
- Overt bleeding producing a hemoglobin decrease ≥ 2 g/dL in 24 hours, confirmed by repeat
- Any overt bleeding deemed by the investigator to necessitate discontinuation of study medication
- QTcF interval > 500 msec or increase in QTc interval of > 60 msec from baseline (confirmed by repeat ECG)
- Medical or surgical treatment for bleeding beyond the application of pressure or cold compresses
- Need for treatment with a strong CYP3A4 inhibitor

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

In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/designee of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Refer to Section 9.2.5 Pregnancy.

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.

### 8.1.2 Stopping Rules

Dosing for all participants will be stopped until safety information can be reviewed if any one of the following criteria is met and confirmed by repeat test as appropriate (a repeat draw must be performed within 24 hours):

- Two or more participants have a related SAE
- Two or more participants have an AE at severe intensity
- One participant with a clinically significant bleeding event (eg, CNS, severe epistaxis, severe hematuria, hematemesis, or GI bleeding) defined as a hemoglobin drop of ≥ 3 grams, a reduction hematocrit by ≥ 30%, or requiring blood transfusion or hemodynamic support to maintain systolic blood pressures
- One participant with serum blood urea nitrogen or creatinine > 2× ULN (confirmed by repeat)
- Two or more participants have QTcF > 500 msec (confirmed by repeat ECG)
- Two or more participants have AST and/or ALT > 5× ULN (confirmed by repeat)
- One participant has AST and/or ALT > 3× ULN AND total bilirubin > 2.0× ULN (confirmed by repeat)
- Two or more participants have a total bilirubin > 3.0× ULN (confirmed by repeat)
- One participant has ALT or AST > 3× ULN (confirmed by repeat) with the appearance or worsening of symptoms felt by the investigator to be potentially related to hepatic injury, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia
- Two or more participants with an SAE or an AE of serious degree occurs in any treatment arm of the study, either within the same group or in different study groups, further dosing in the study for all groups will be paused until a full safety review can be conducted, and make a determination whether or not further dosing in this group or in any other study group shall proceed

The Sponsor and investigator may decide to halt dosing for reasons not defined above, including but not limited to, observing a single SAE in individual participants and/or observing trends during the study. If any of the listed stopping rules are met on review of the data, dosing will not be resumed.

If any of the above criteria are met, the study will be put on hold and all safety data available across the study will be evaluated to estimate the risk of proceeding. Upon conclusion of this in-depth safety review, one of the following recommendations will be made:

- To continue with the study as planned (ie, there are no clinically significant safety concerns);
- To continue with the study by repeating the current treatment arm in more participants. Any restart after the stopping rules have been met will require prior approval of a substantial amendment providing justification for the restart;
- To continue with a modified dose regimen deemed necessary by safety, tolerability, or PK analysis;

- To terminate the study.

## 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 study allocation. 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.

### *9.1.1 Imaging Assessment for the Study*

At the sponsor's discretion, scans may be collected for review.

This is not applicable for this study.

## 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 are specified in Appendix 3**

### *9.2.1 Time Period and Frequency for Collecting AE and SAE Information*

Appendix 1 in the IB (BMS-986141) and Section 4.8 in the Summary of Product Characteristics (aspirin and ticagrelor) represent the Reference Safety Information, and they are used to determine expectedness of SAEs for expedited reporting.

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures 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, (eg, a follow-up skin biopsy).

- 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 module.
- 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 or designee within 24 hours of updated information 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 Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR 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 for 5 half-lives (5 days) plus 30 days (duration of ovulatory cycle), for a total of 35 days after study 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.

If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

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 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) ALT or AST elevation > 3× ULN

AND

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

AND

3) No other immediately apparent possible causes of aminotransferase 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, ECG, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or SAE, as appropriate, and reported accordingly.

### 9.3 Overdose

For this study, any dose of BMS-986141 greater than 4 mg and any dose of aspirin greater than 75 mg within a 24-hour time period will be considered an overdose. As the standard of care for ticagrelor is 90 mg given BID, any dose of ticagrelor greater than 180 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).

#### 9.4.1 Physical Examinations

Refer to Schedule of Activities (Section 2).

##### 9.4.1.1 Medical Photography

Starting on Day 1, standard baseline photographs of any area with clinical findings will be taken at the discretion of the Principle Investigator. If there are any changes with the affected areas or new clinical findings, additional photographs will be obtained. Photographs will not be needed if there is no clinical finding 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 must be available prior to BMS-986141 dosing.

| | |
|---|---|
| **Hematology** | |
| Red blood cells | |
| Hemoglobin | |
| Hematocrit | |
| Total leukocyte count, including differential | |
| Platelet count | |
| **Chemistry** | |
| AST<br>ALT<br>Total bilirubin<br>Direct bilirubin<br>Alkaline phosphatase<br>Lactate dehydrogenase<br>Creatinine<br>Blood urea nitrogen<br>Uric acid<br>Fasting glucose | Total protein<br>Albumin<br>Sodium<br>Potassium<br>Chloride<br>Calcium<br>Phosphorus<br>Magnesium<br>Creatine kinase |
| **Coagulation** | |
| INR | |
| aPTT | |
| Prothrombin time | |
| Platelet count | |
| **Urinalysis** | |
| Protein | |
| Glucose | |
| Blood | |
| Leukocyte esterase | |
| Specific gravity | |
| pH | |
| Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick | |
| **Serology** | |

| |
|---|
| Serum for hepatitis C antibody, hepatitis B surface antigen, HIV-1 and -2 antibodies (screening only). See Appendix 7 for hepatitis B serologic test results interpretation. |
| **Other Analyses** |
| Test for drugs of abuse and alcohol (urine or serum) (screening and Day 1) |
| Pregnancy test (WOCBP only: screening, predose, clinic discharge) |
| Follicle-stimulating hormone (postmenopausal women only; screening) |

### *9.4.5 Imaging Safety Assessment*

Not applicable.

## 9.5 Pharmacokinetics

Pharmacokinetic characteristics of BMS-986141, metabolite BMT-162856, ASA, salicylic acid, and ticagrelor will be observed from plasma concentration versus time data. Potential correlation between drug exposures and thrombus formation in an ex vivo porcine aortic thrombosis chamber and other biomarkers/PD markers will be explored. The PK samples being collected will provide concentrations near Tmax.

Table 9.5-1 (Treatment Arm 1), Table 9.5-2 (Treatment Arm 2), Table 9.5-3 (Treatment Arm 3), and Table 9.5-4 (Treatment Arm 4) list the sample schedule to be following for the PK assessments of BMS-986141, ticagrelor, and ASA.

**Table 9.5-1: Pharmacokinetic Sampling Schedule for BMS-986141 and Ticagrelor (Treatment Arm 1)**

| Study Day of Sample Collection | Event | Time (Relative To BMS-986141 Dose)Hour: Min | BMS-986141 and BMT-162856 Blood Sample for Plasma PK Profiling | Ticagrelor Blood Sample for Plasma PK Profiling |
|---|---|---|---|---|
| 1 | predose[a] | -02:00 | X | X |
| 1 | | 02:00 | X | X |
| 2 | | 24:00 | X | X |

[a] The predose sample should be collected within 2 hours prior to BMS-986141 administration.
Abbreviation: PK = pharmacokinetic

**Table 9.5-2: Pharmacokinetic Sampling Schedule for BMS-986141 and Acetylsalicylic Acid (Treatment Arm 2)**

| Study Day of Sample Collection | Event | Time (Relative To BMS-986141 Dose)Hour: Min | BMS-986141 and BMT-162856 Blood Sample for Plasma PK Profiling | Acetylsalicylic Acid and Salicylic Acid Blood Sample for Plasma PK Profiling |
|---|---|---|---|---|
| 1 | predose[a] | -02:00 | X | X |
| 1 | | 02:00 | X | X |
| 2 | | 24:00 | X | X |

[a] The predose sample should be collected within 2 hours prior to BMS-986141 administration.
Abbreviation: PK = pharmacokinetic

**Table 9.5-3: Pharmacokinetic Sampling Schedule for BMS-986141, Ticagrelor, and Acetylsalicylic Acid (Treatment Arm 3)**

| Study Day of Sample Collection | Event | Time (Relative To BMS-986141 Dose)Hour: Min | BMS-986141 and BMT-162856 Blood Sample for Plasma PK Profiling | Ticagrelor Blood Sample for Plasma PK Profiling | Acetylsalicylic Acid and Salicylic Acid Blood Sample for Plasma PK Profiling |
|---|---|---|---|---|---|
| 1 | predose[a] | -02:00 | X | X | X |
| 1 | | 02:00 | X | X | X |
| 2 | | 24:00 | X | X | X |

[a] The predose sample should be collected within 2 hours prior to BMS-986141 administration.
Abbreviation: PK = pharmacokinetic

**Table 9.5-4: Pharmacokinetic Sampling Schedule for BMS-986141 (Treatment Arm 4)**

| Study Day of Sample Collection | Event | Time (Relative To BMS-986141 Dose)Hour: Min | BMS-986141 and BMT-162856 Blood Sample for Plasma PK Profiling |
|---|---|---|---|
| 1 | predose | 00:00 | X |
| 1 | | 02:00 | X |
| 2 | | 24:00 | X |

Abbreviation: PK = pharmacokinetic

The plasma samples will be analyzed for BMS-986141, ASA, salicylic acid, and ticagrelor by validated liquid chromatography mass spectrometry/mass spectrometry (LC-MS/MS) assays. BMT-162856, a metabolite of BMS-986141, will be analyzed by a qualified LC-MS/MS assay. In addition, plasma samples will be archived for potential metabolite analysis, if the need arises and to the extent possible.

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

## 9.6 Pharmacodynamics

Refer to Section 9.8.

[redacted]

## 9.8 Biomarkers

Thrombus formation will be determined using the Badimon chamber. Venous blood will be collected from study participants through a cannula set attached to extension tubing. The tubing will be connected to a series of 3 perfusion chambers containing porcine aorta as a thrombogenic surface. A pump placed distal to the chambers will maintain unidirectional flow at a rate of 10 mL/min. The rheologic conditions in the first chamber stimulate those of patent arteries (low shear rate, approximately 212 $s^{-1}$), and those in the second and third chambers simulate those of stenosed arteries (high shear rate, approximately 1690 $s^{-1}$). Each perfusion study will last for 5 minutes. Immediately after each perfusion, porcine strips with thrombus attached will be

removed and fixed, and total thrombus area will be assessed by morphometrical analysis. [redacted]

Aortic strip analysis will be performed blinded. Aortic strips will be assigned and stored with a unique sample number unrelated to the participant number. Aortic stripes are then processed by the histology department, who are blinded to the study entirely, and analyzed at a later date by an operator blinded to the aortic strip linked sample numbers. Sample linkage will be kept securely in the study site.

Circulating biomarker assessment for this chamber study focuses primarily on PD biomarkers. [redacted]

In addition, serum samples will be collected for assessment of SARS-CoV-2 serology.

Blood will be drawn at the times indicated in Table 9.8-1 and Table 9.8-2. Further details of blood collection and processing will be provided to the site in the procedure manual.

**Table 9.8-1: Biomarker Sampling Schedule - Treatment Arms 1, 2, and 3**

| Study Day of Sample Collection | Event | Time (Relative To BMS-986141 Dose) Hour:Min | [redacted] | [redacted] | [redacted] | Serum for SARS-CoV-2 serology |
|---|---|---|---|---|---|---|
| 1 | predose | -02:00 | [redacted] | [redacted] | [redacted] | X |
| 1 | | 02:00 | [redacted] | [redacted] | [redacted] | |
| 2 | | 24:00 | [redacted] | [redacted] | [redacted] | |

Abbreviations: [redacted]

**Table 9.8-2: Biomarker Sampling Schedule - Treatment Arm 4**

| Study Day of Sample Collection | Event | Time (Relative To BMS-986141 Dose) Hour:Min | [redacted] | [redacted] | [redacted] | Serum for SARS-CoV-2 serology |
|---|---|---|---|---|---|---|
| 1 | predose | 00:00 | [redacted] | [redacted] | [redacted] | X |
| 1 | | 02:00 | [redacted] | [redacted] | [redacted] | |
| 2 | | 24:00 | [redacted] | [redacted] | [redacted] | |

Abbreviations: [redacted]

### *9.8.1 Additional Research Collection*

This protocol will include residual sample storage.

**For All US Sites:**

Not applicable.

**For non-US Sites**

Additional research is optional for all study participants, except where retention and/or collection is prohibited by local laws or regulations, ethics committees, or institutional requirements.

This collection for additional research is intended to expand the translational R&D capability at Bristol-Myers Squibb, 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.

[redacted] biomarker, and [redacted] (see Table 9.8.1-1) will also be retained for additional research purposes.

Samples kept for future research will be stored at the [redacted] or an independent, BMS-approved storage vendor.

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.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

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 |
| Whole blood/DNA | All |
| Plasma serum biomarkers | All |

Abbreviation: PK = pharmacokinetic

### *9.8.2 Other Assessments*

Not applicable.

## 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 sample size for this study is not based on statistical power, but based on consideration of the precision of the estimate of the effect of BMS-986141 alone and as add on to aspirin, ticagrelor, or the aspirin/ticagrelor combination, on thrombus formation in an ex vivo porcine aortic thrombosis chamber model as compared to pretreatment.

The half-width of the 95% CI of the change from baseline in thrombus area on the log scale after administration of BMS-986141 will be 0.146 or 0.188 if there are 15 or 10 participants per arm, respectively. This calculation assumes that the thrombus area is log-normally distributed and the change from baseline on the log scale has a standard deviation of 0.263 as observed in CV004-007.

The following table provides examples of 95% CIs of the true percent reduction in thrombus area after administration of BMS-986141, assuming the true percent reduction (percent decrease from baseline) is 15%, 20%, or 30%, and the sample size is 15 per arm or 10 per arm.

| Sample Size per Arm | True Reduction from Baseline | Change from Baseline on Log Scale (95% CI) | Geometric Mean Ratio to Baseline (95% CI) |
|---|---|---|---|
| 15 | 15% | -0.163 (-0.309, -0.017) | 0.85 (0.73, 0.98) |
| 15 | 20% | -0.223 (-0.369, -0.077) | 0.80 (0.69, 0.93) |
| 15 | 30% | -0.357 (-0.503, -0.211) | 0.70 (0.60, 0.81) |
| 10 | 30% | -0.357 (-0.545, -0.169) | 0.70 (0.58, 0.84) |

Approximately 55 participants (15 participants in Treatment Arms 1, 2, and 3, and 10 participants in Treatment Arm 4) are planned to be dosed with BMS-986141.

## 10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

| Population | Description |
|---|---|
| Enrolled | All participants who sign informed consent |
| Treated | The Treated Population is a subset of the Enrolled Population including all participants who received BMS-986141. |
| Pharmacokinetic | The PK Population is a subset of the Treated Population. The PK Population includes all participants who received BMS-986141 and had any available concentration-time data |
| Biomarker | The Biomarker Population is a subset of the Treated Population. The Biomarker Population includes all participants who received BMS-986141 and had any available biomarker data. |

## 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 of the primary and secondary endpoints.

### *10.3.1 Efficacy Analyses*

Not applicable.

### *10.3.2 Safety Analyses*

All safety analyses will be performed on the Treated Population.

| Endpoint | Statistical Analysis Methods |
|---|---|
| Secondary:<br>AEs, clinical laboratory | Descriptive summaries will be presented for continuous variables using number of participants (N), mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will utilize counts |

| | |
|---|---|
| values, vital signs, ECGs, or other safety biomarkers | and percentages. All recorded AEs will be listed and tabulated by system organ class, preferred term, treatment arm, and treatment. Vital signs, ECGs, and clinical laboratory test results will be listed and summarized by planned time point, treatment arm, and treatment. Marked abnormal clinical laboratory test results will be summarized by treatment arm and treatment. Any significant physical examination findings will be listed. Electrocardiogram readings will be summarized by planned time point, treatment arm, and treatment, and investigator-identified abnormalities, if present, will be listed. |

### *10.3.3 Other Analyses*

| Endpoint | Statistical Analysis Methods |
|---|---|
| Primary:<br>Change from baseline in thrombus area (post-treatment with BMS-986141 vs. pretreatment) | An analysis of variance will be performed on the natural logarithm (ln)-transformed thrombus area using general linear mixed effects models separately by shear rates (Low or High) with perfusion run (baseline, 2 hours, and 24 hours) as fixed effects and participant as a random effect. A supplemental analysis of variance will be performed on the natural ln-transformed thrombus area using general linear mixed effects models separately by shear rates (Low or High) with treatment arm, perfusion run (baseline, 2 hours, and 24 hours) as fixed effects and participant as a random effect. Means, mean differences from baseline, and the 95% CI of mean differences on the log scale will be estimated from the models and be exponentiated to express the results as geometric means, geometric mean ratios to baseline, and the 95% CI of geometric mean ratios on the original scale. All thrombosis chamber endpoints will be listed, plotted and summarized by treatment arm, shear rate, and perfusion run. |

[redacted] Summary statistics for each of the biomarkers and their corresponding percent changes from baseline will be tabulated by treatment arm, shear rate, and perfusion run. Plots of mean values of biomarkers, as well as geometric mean percent changes from baseline versus shear rate and perfusion run will be provided for each treatment arm. Potential correlation between BMS-986141 exposure and thrombus formation in an ex vivo porcine aortic thrombosis chamber and other biomarkers/PD markers will be explored.

Summary statistics for PK concentrations of BMS-986141, metabolite BMT-162856, ASA, salicylic acid, and ticagrelor will be tabulated.

[redacted]

### *10.3.4 Interim Analyses*

Not applicable.

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# 12 APPENDICES

## APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

| Term | Definition |
|---|---|
| [redacted] | [redacted] |
| ADP | adenosine diphosphate |
| AE | adverse event |
| ALT | alanine aminotransferase |
| AP | agonist peptide |
| aPTT | activated partial thromboplastin time |
| ASA | acetylsalicylic acid |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| AUC(0-24) | area under the concentration-time curve from time zero to 24 hours after dose |
| AUC(TAU) | area under the concentration-time curve over the dosing interval |
| BID | bis in die, twice daily |
| BMI | body mass index |
| BMS | Bristol-Myers Squibb |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CLTp | total plasma clearance |
| Cmax | maximum observed concentration |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRF | case report form, paper or electronic |
| CYP | cytochrome P450 |
| DILI | drug-induced liver injury |
| DNA | deoxyribonucleic acid |
| EC50 | concentration required for 50% efficacy |
| EC80 | concentration that gives 80% of Emax |
| ECAT | cyno-electrically-mediated carotid arterial thrombosis |
| ECG | electrocardiogram |
| F | oral bioavailability |

| Term | Definition |
|---|---|
| HIV | human immunodeficiency virus |
| IB | investigator's brochure |
| IC50 | concentration at which 50% inhibition observed |
| IEC | Independent Ethics Committee |
| IMP | investigational medicinal products |
| INR | international normalized ratio |
| IP | investigational product |
| IRB | institutional review board |
| LC-MS/MS | liquid chromatography mass spectrometry/mass spectrometry |
| PAR1 | protease-activated receptor 1 |
| PAR2 | protease-activated receptor 2 |
| PAR4 | protease-activated receptor 4 |
| PD | pharmacodynamic(s) |
| PK | pharmacokinetic(s) |
| PMA | platelet-monocytes aggregates |
| QTcF | QT corrected for HR using the Fridericia formula |
| SAE | serious adverse event |
| sCD40L | soluble CD40 ligand |
| SDD | spray-dried dispersion |
| sP-selectin | soluble platelet selectin |
| SUSAR | suspected, unexpected serious adverse reaction |
| T-HALF | Half-life |
| TIA | transient ischemic attack |
| Tmax | time of maximum observed concentration |
| ULN | upper limit of normal |
| Vss | volume of distribution at steady state |
| vWF | von Willebrand factor |
| 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 CRF 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 on 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 the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation, etc) that is likely to affect, to a significant degree one or more of the following: (1) the physical, safety or mental integrity of one or more subjects/participants; (2) the scientific value of the trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP Regulation(s) or Trial protocol(s).

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/participants. 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/participants 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/participants.

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/participants 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/participants 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/participants 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 by subjects/participants, 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/participants, 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/participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects'/participants' signed ICF and, in the US, the subjects'/participants' signed HIPAA Authorization.

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

The rights, safety, and well-being of the study subjects/participants 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 BMS-986141, ticagrelor, and aspirin (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:<br>• amount received and placed in storage area<br>• amount currently in storage area<br>• label identification number or batch number<br>• amount dispensed to and returned by each participant, including unique participant identifiers<br>• amount transferred to another area/site for dispensing or storage<br>• nonstudy disposition (eg, lost, wasted)<br>• amount destroyed at study site, if applicable<br>• amount returned to BMS<br>• retain samples for bioavailability/bioequivalence/biocomparability, if applicable<br>• 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.

The confidentiality of records that could identify subjects/participants 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. 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.

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).<br><br>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 sites stock or commercial supply, or a specialty pharmacy) | It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures. |

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

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.

- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of 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

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.

## SCIENTIFIC PUBLICATIONS

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.

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any principal investigator, sub-investigator or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable subjects with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND

4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

# 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.

**Events Meeting the AE Definition**

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term

**Events NOT Meeting the AE Definition**

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

## DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

## 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)<br>NOTE:<br>The following hospitalizations are not considered SAEs in BMS clinical studies:<br>• 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)<br>• elective surgery, planned prior to signing consent<br>• admissions as per protocol for a planned medical/surgical procedure<br>• routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)<br>• medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases<br>• admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)<br>• 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 [e.g., 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.) |

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see section 9.2.5 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy should be reported as SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

## EVALUATING AES AND SAES

**Assessment of Causality**

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**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) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the eCRF.
  - The paper SAE Report Form is only intended as a back-up option when the electronic data capture (EDC) system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile (fax) transmission
    - When paper forms are used, the original paper forms are to remain on site
- Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission

**SAE Email Address: Refer to Contact Information list.**

**SAE Facsimile Number: Refer to Contact Information list.**

**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.

### End of Relevant Systemic Exposure

- End of relevant systemic exposure is the time point where the IMP or any active major metabolites has decreased to a concentration that is no longer considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins

from the no-observed adverse effect level (NOAEL) or the time required for 5 half-lives of the IMP to pass.

## METHODS OF CONTRACEPTION

One of the highly effective methods of contraception listed below should be continued for a minimum of 9 days (5 half-lives of BMS-986141, 5 half-lives of aspirin and ticagrelor are shorter than 9 days) post-treatment completion.

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 and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b]
  - oral (birth control pills)
  - intravaginal (vaginal birth control suppositories, rings, creams, gels)
  - transdermal
- Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy

- Progestogen-only hormonal contraception associated with inhibition of ovulation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b]
  - oral
  - injectable
- Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy

**Highly Effective Methods That Are User Independent**

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS) (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol) [b,c]
- Bilateral tubal occlusion

- Vasectomized partner

A vasectomy is a highly effective contraception method provided that the participant 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.*

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy
- 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
- Periodic abstinence (including but not limited to calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study.

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 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

**Unacceptable Methods of Contraception**

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal(coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)
- 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 (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)

## 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 three (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 (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., 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 (e.g., current cocaine use despite recognition of cocaine-induce 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 six months, some use of the substance and some symptoms of dependence.

In Full Remission: During the past six 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 one (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 (e.g., 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 (e.g., driving an automobile or operating a machine when impaired by substance use).
   3. Recurrent substance-related legal problems (e.g., 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 (e.g., 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.

## APPENDIX 6 CYP3A4 AND CYP2B6 GUIDANCE

The lists below are not meant to be all inclusive. Please consult individual drug labels for further information. Additional information is also available at:

https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

**Table 1: Classification of In Vivo Inhibitors of CYP Enzymes**

| CYP Enzymes | Strong Inhibitors[a] ≥ 5-fold Increase in AUC or > 80% Decrease in CL | Moderate Inhibitors[b] ≥ 2 but < 5-fold Increase in AUC or 50%-80% Decrease in CL | Weak Inhibitors[c] ≥ 1.25 but < 2-fold Increase in AUC or 20%-50% Decrease in CL |
|---|---|---|---|
| CYP3A | Boceprevir, clarithromycin, conivaptan, grapefruit juice,[d] indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil,[e] nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole | Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice,[d] imatinib, verapamil | Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo,[f] goldenseal,[f] isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton |

Please note that this is not an exhaustive list.

[a] A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold.

[b] A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.

[c] A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 5-fold.

[d] The effect of grapefruit juice varies widely among brands and is concentration, dose, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).

[e] Withdrawn from the United States market because of safety reasons.

[f] Herbal product.

Abbreviations: AUC = area under the concentration-time curve; CL = clearance; CYP = cytochrome P450

**Table 2: Classification of In Vivo Inducers of CYP Enzymes**

| CYP Enzymes | Strong Inducers ≥ 80% Decrease in AUC | Moderate Inducers 50%-80% Decrease in AUC | Weak Inducers 20%-50% Decrease in AUC |
|---|---|---|---|
| CYP3A | Avasimibe,[a] carbamazepine, phenytoin, rifampin, St. John's wort[b] | Bosentan, efavirenz, etravirine, modafinil, nafcillin | Amprenavir, aprepitant, armodafinil, echinacea,[c] pioglitazone, prednisone, rufinamide |

Please note that this is not an exhaustive list.

[a] Not a marketed drug.

[b] The effect of St. John's wort varies widely and is preparation dependent.

[c] Herbal product.

Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome P450.

**Table 3: Examples of Sensitive In Vivo CYP Substrates and CYP Substrates with Narrow Therapeutic Range**

| CYP Enzymes | Sensitive Substrates[a] | Substrates with Narrow Therapeutic Range[b] |
|---|---|---|
| CYP3A | Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil | Alfentanil, astemizole,[c] cisapride,[c] cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine[c] |
| CYP2B6 | Bupropion, efavirenz | |

Please note that this is not an exhaustive list.

[a] Sensitive CYP substrates refers to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor.

[b] CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).

[c] Withdrawn from the United States market because of safety reasons.

Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome P450

# APPENDIX 7 INTERPRETATION OF HEPATITIS B SEROLOGICAL TEST RESULTS

As study treatment in this study is expected to demonstrate immunosuppressive effects, it is imperative to carefully evaluate and exclude participants with potentially active hepatitis B infection. For this reason, in order to fully evaluate a participant's eligibility for enrollment, the exclusion criterion (see Section 6.2) requires interpretation of data from 3 standard tests for hepatitis B, ie, measurement of hepatitis B surface antigen (HBsAg), hepatitis B core antigen antibody (anti-HBc), and hepatitis B surface antibody (anti-HBs).

Participant's eligibility for enrollment should be assessed as described below. Participants that are:

- Hepatitis B serological test negative (neg) for all results may be included in the study
- HBsAg (neg), anti-HBc (neg), and anti-HBs positive (POS) may be included in the study (immunized due to hepatitis B vaccination)
- HBsAg (neg), anti-HBc (POS), and anti-HBs (POS) are to be excluded from the study (immune due to natural infection exposure)
- Participants that are HBsAg (POS) are excluded from the study (acute or chronic infection)
- Participants that are anti-HBc (POS) are excluded from the study (acute or chronic infection)
- Participants that are HBsAg (neg), anti-HBc (POS), and anti-HBs (neg) are to be excluded from the study (interpretation unclear)

Please also refer to the following "Interpretation of Hepatitis B Serologic Test Results" provided by the Department of Health and Human Services, Centers for Disease Control and Prevention.

# Interpretation of Hepatitis B Serologic Test Results

Hepatitis B serologic testing involves measurement of several hepatitis B virus (HBV)-specific antigens and antibodies. Different serologic "markers" or combinations of markers are used to identify different phases of HBV infection and to determine whether a patient has acute or chronic HBV infection, is immune to HBV as a result of prior infection or vaccination, or is susceptible to infection.

| | | |
|---|---|---|
| **HBsAg**<br>**anti-HBc**<br>**anti-HBs** | negative<br>negative<br>negative | Susceptible |
| **HBsAg**<br>**anti-HBc**<br>**anti-HBs** | negative<br>positive<br>positive | Immune due to natural infection |
| **HBsAg**<br>**anti-HBc**<br>**anti-HBs** | negative<br>negative<br>positive | Immune due to hepatitis B vaccination |
| **HBsAg**<br>**anti-HBc**<br>**IgM anti-HBc**<br>**anti-HBs** | positive<br>positive<br>positive<br>negative | Acutely infected |
| **HBsAg**<br>**anti-HBc**<br>**IgM anti-HBc**<br>**anti-HBs** | positive<br>positive<br>negative<br>negative | Chronically infected |
| **HBsAg**<br>**anti-HBc**<br>**anti-HBs** | negative<br>positive<br>negative | Interpretation unclear; four possibilities:<br>1. Resolved infection (most common)<br>2. False-positive anti-HBc, thus susceptible<br>3. "Low level" chronic infection<br>4. Resolving acute infection |

**Adapted from:** A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. Part I: Immunization of Infants, Children, and Adolescents. MMWR 2005;54(No. RR-16).

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Centers for Disease Control and Prevention
*Division of Viral Hepatitis*

www.cdc.gov/hepatitis

- **Hepatitis B surface antigen (HBsAg):** A protein on the surface of hepatitis B virus; it can be detected in high levels in serum during acute or chronic hepatitis B virus infection. The presence of HBsAg indicates that the person is infectious. The body normally produces antibodies to HBsAg as part of the normal immune response to infection. HBsAg is the antigen used to make hepatitis B vaccine.
- **Hepatitis B surface antibody (anti-HBs):** The presence of anti-HBs is generally interpreted as indicating recovery and immunity from hepatitis B virus infection. Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B.
- **Total hepatitis B core antibody (anti-HBc):** Appears at the onset of symptoms in acute hepatitis B and persists for life. The presence of anti-HBc indicates previous or ongoing infection with hepatitis B virus in an undefined time frame.
- **IgM antibody to hepatitis B core antigen (IgM anti-HBc):** Positivity indicates recent infection with hepatitis B virus (≤6 mos). Its presence indicates acute infection.

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## APPENDIX 9 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

**Overall Rationale for the Protocol Amendment 01, 18-Mar-2021**

The purpose of this amendment is to change the dosage and dose formulation of BMS-986141 and add restrictions for enrollment if participants received the SARS-CoV-2 vaccine. BMS-986141 will be dosed as a tablet and participants will receive 4 mg tablets as their dose.

| SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01 | | |
|---|---|---|
| **Section Number & Title** | **Description of Change** | **Brief Rationale** |
| Section 5.1: Overall Design | Changed BMS-986141 to a 4 mg dose. | Dose was changed to 4 mg. |
| Section 5.1: Study Design Schematic | Changed BMS-986141 to a 4 mg dose. | Dose was changed to 4 mg. |
| Section 5.4: Scientific Rationale for Study Design | Changed BMS-986141 to a 4 mg dose. | Dose was changed to 4 mg. |
| Section 5.5: Justification for Dose | Changed BMS-986141 to a 4 mg dose. | Dose was changed to 4 mg. |
| Section 7: Treatment | Changed BMS-986141 to a 4 mg tablet. | Dose was changed to 4 mg and formulation was changed to a tablet. |
| Table 7.1: Study Treatments for CV006037 | Changed BMS-986141 to a 4 mg tablet. | Dose was changed to 4 mg and formulation was changed to a tablet. |
| Section 7.1: Treatments Administered | Removed wording for the inclusion of a rinse. | Only 240 mL of water will be given with the tablet dose; rinse is no longer necessary. |
| Table 7.1-1: Selection and Timing of Dose | Changed BMS-986141 to a 4 mg dose. | Dose was changed to 4 mg. |
| Section 7.7.1: Prohibited and/or Restricted Treatments | Added information and restriction for SARS-CoV-2 vaccine. | Clarified that SARS-CoV-2 vaccine requirements for enrollment. |
| Section 9.3: Overdose | Changed BMS-986141 to a 4 mg dose. | Dose was changed to 4 mg. |
| All | Minor formatting and typographical corrections throughout. | These have been corrected but not summarized here. |