Official Title of Study:

A Global, Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of BMS-986177, an Oral Factor XIa Inhibitor, for the Prevention of New Ischemic Stroke or New Covert Brain Infarction in Patients Receiving Aspirin and Clopidogrel Following Acute Ischemic Stroke or Transient Ischemic Attack (TIA)

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Clinical Protocol CV010031

A Global, Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of BMS-986177, an Oral Factor XIa Inhibitor, for the Prevention of New Ischemic Stroke or New Covert Brain Infarction in Patients Receiving Aspirin and Clopidogrel Following Acute Ischemic Stroke or Transient Ischemic Attack (TIA)

AXIOMATIC-SSP

Antithrombotic treatment with factor **XI**a inhibition to **O**ptimize **M**anagement of **A**cute **T**hromboembo**lic** events in **S**econdary **S**troke **P**revention

Revised Protocol 06

[redacted]

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BMS-986177 is being co-developed under a collaboration agreement between Bristol-Myers Squibb Company (BMS) and Janssen Pharmaceuticals, Inc. (Janssen)

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 06	09-Oct-2020	• Increased NIHSS score inclusion criterion for qualifying event from ≤5 to ≤7. • Removed use of thrombolytic therapy/mechanical thrombectomy for treatment of the index event from exclusion criteria and added to inclusion criteria to be permitted under specified conditions. • Added intracranial artery stenosis requiring angioplasty within 90 days to the exclusion criteria. • Clarified that treated aneurysms without history of intracranial bleed are permitted. • Clarified that only complete occlusion of a cervical carotid artery or an intracranial artery on the ipsilateral site and proximal to the index lesion are exclusionary for the study. • Clarified UFH or LMWH for DVT prophylaxis allowance prior to enrollment. • Updated INR exclusion requirement from INR >1.7 to INR >1.5. • Updated exclusion criteria to include history of 12-lead ECG findings requiring exclusion. • Added exclusion criterion of known SARS-CoV-2 infection within 4 weeks of screening and associated conditions. • Clarified that a clinical (standard-of-care) MRI scan can be used as the baseline MRI provided that the clinical MRI protocol and scanner have been pre-approved by the central imaging vendor. • Removed requirement of baseline MRI within 48 hours of index event and prior to randomization and provided instruction regarding instances where the baseline MRI cannot be performed within 48 hours of the index event and before randomization. • Expanded the available window for the baseline MRI for instances where the MRI cannot be performed within 48 hours of the index event and prior to randomization to up to 72 hours after the onset of the index event and up to 24 hours after randomization • Removed +10 day visit window from Day 90 visit and added instruction regarding performance of the Day 90 MRI when impacted by the COVID-19 pandemic. • Added statement that alternative measures can be considered to obtain required visit assessments for participants who are unable or not permitted to attend an onsite visit due to the COVID-19 pandemic as local regulatory requirements permit. • Updated Day 60 visit description to ease telephone contact requirement for participants who completed required assessments at Day 60 site visit and removed requirement of reviewing Day 60 clinical laboratory results with participant.

Document	Date of Issue	Summary of Change
		• Added statement that the DMC recommendation regarding the Day 60 clinical laboratory sample will be communicated to the investigator by the Sponsor. • Updated the milestone requirement for DMC review to decide on inclusion of the 200-mg BID dose arm. • Removed contrast use restriction for the collection of the study MRIs to allow for contrast agent administration as per investigator discretion and local clinical practice. • Revised statement that study drug BMS-986177 must be permanently discontinued if thrombolytic therapy or thrombectomy is used for the treatment of a new stroke during the study to allow for only a temporary interruption and restart of BMS-986177 if pre-specified conditions are met. • Modified required duration of SAE collection from 7 days after discontinuation of dosing to through the follow-up period. • Simplified pharmacokinetic and pharmacodynamic sampling schedules. • Added biomarkers related to SARS-CoV-2 infection status or related pathophysiological pathways to exploratory biomarker assessments. • Provided sample size estimations for the study without inclusion of the 200-mg BID dose arm. • Updated Appendix 2 to specify that other means of remote monitoring approved by the Sponsor and as local regulatory requirements permit can be considered. • Other changes made related to typographical errors, clarifications, changes in terminology, and alignment to other key study documents.
Revised Protocol 05	24-Aug-2019	• Removed 3 QD doses groups (lowest 25 mg QD dose is maintained); keeping all BID doses. Accordingly, the sample size of the study is reduced and primary objective is updated (dose-response trend is retained; MED and ED90 assessment is removed) • Primary analysis MCP-MOD (include placebo and 25 mg QD as lowest dose) o Additional exploratory analyses using the 25 mg QD dose and control • Response-adapted randomization (RAR) initially proposed has been replaced with a non-RAR randomization schema • Title of the protocol was changed to reflect the new design • Removed RAR interim analyses, added administrative interim analyses • Removed RNA and miRNA sample collection and testing
Revised Protocol 04	03-May-2019	• Updated exclusion criteria to exclude participants with arteriovenous malformation (AVM)

Document	Date of Issue	Summary of Change
Revised Protocol 03	05-Apr-2019	• Allow clopidogrel loading doses of 300 mg to 600 mg prior to signing informed consent • Removal of aortic arch atheroma >4 mm in thickness from vascular imaging criteria and updated criteria for atherosclerotic plaque • Added exploratory objective to assess the incidence and characteristics of cerebral microbleeds (CMBs), hemorrhagic transformation of ischemic stroke and asymptomatic intracranial bleeding on Day 90 • Added specifics regarding petechiae on brain imaging • Clarified that MRI is not required to determine study eligibility • Clarified assessments to be completed for participants who discontinue study treatment • Updated PK characteristics table to include estimate of renal clearance and impact of renal impairment • Added instructions for missed doses • Added details for brief physical exam • Provided guidance for the management of bleeding events • Modified the PK and PD sample collection window for the 12-hour post-first dose time point and the requirement of a 12- and 24-hour PK/PD sample collection for TIA subjects on Day 1. • Clarified assessments to be completed at screening *vs.* prior to dosing on Day 1 • Added scenarios where the DMC and the RAR vendor will receive unblinded data for safety assessment • Added new appendices for strong CYP3A inhibitors and inducers • Added guidance for use of thrombolytic therapy for the treatment of new stroke, including availability of unblinding • Reduced the window for collection of information on medications taken prior to study drug from 30 days to 7 days • Reduced the window for SAE collection after discontinuation of study medication from 30 days to 7 days • Reorganized statistical analysis sections to tabular form matching endpoint with statistical method • Corrected/clarified discrepant items
Administrative Letter 01	27-Nov-2018	Correcting a typo in the summary of Change column of the document history

Document	Date of Issue	Summary of Change
Revised Protocol 02	31-Oct-2018	• Appendix 3 updated for Adverse Events (AE) definitions and details • Day 60 ±7 central clinical laboratory sample collection added • DMC review for the first 450 and 600 subjects added to make recommendation regarding collection of clinical laboratory samples • Corrected/clarified items (IP designation, PK/PD sample time and collection window)
Revised Protocol 01	20-Sep-2018	• Updated based on [redacted] Steering Committee feedback • Study Design changes for clopidogrel loading dose and staggered approach for high dose groups randomization • Corrected/clarified discrepant items
Original Protocol	13-Jul-2018	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 06:

The purpose of Revised Protocol 06 is to incorporate Steering Committee and investigator feedback for modification of selected study eligibility criteria. This includes increasing the National Institute of Health Stroke Scale (NIHSS) at randomization from ≤5 to ≤7 and permitting intravenous thrombolytic therapy, as well as mechanical thrombectomy, for the index event provided conditions are met. These modified criteria reflect a broader population that is closer to clinical practice. In addition, the international normalized ratio (INR) threshold prior to study treatment administration has been lowered from ≤ 1.7 to < 1.5 for all participants to ensure the safety of the study population, which is now permitted to receive thrombolytic therapy and/or mechanical thrombectomy for acute treatment of the index stroke. To accommodate for potential instances where the baseline study MRI cannot be completed within 48 hours, the window for the baseline study MRI has been expanded to up to 72 hours after the onset of the index event with the condition that subjects will need to be dosed within the 48-hour randomization window. To accommodate for regional and institutional practices in study-related MRI acquisition, the administration of contrast agents is permitted as per investigator discretion. Specific to COVID-19, an exclusion criterion was added for the safety of study participants and site personnel. In addition, exploratory research was modified to include biomarkers related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection to support advancing the understanding of the impact of SARS-CoV-2 on the study population, BMS-986177, and cardiovascular disease.

Based on site feedback, the pharmacokinetic and pharmacodynamic sampling requirements have been simplified to facilitate sample collection.

In addition, the SAE collection period has been extended through the follow-up period in order to standardize post-randomization SAE collection with NSAE collection. Previously, SAEs were to be collected for 7 days after discontinuation of dosing.

In an effort to enable flexibility and preserve collection of key study assessments that may be impacted by the COVID-19 pandemic, instructions were added to provide guidance regarding study assessments, including performance of the Day 90 MRI, collection of other onsite assessments that can be conducted remotely (eg, central laboratory tests), and remote monitoring considerations.

Other changes are administrative changes such as typographical errors, clarifications, changes in terminology, and alignment to other key study documents.

The changes made to the protocol are not anticipated to have a significant impact on the benefit-risk of the trial participants, and do not impact the integrity of the study.

The table below highlights the key changes made to the body of the protocol. The changes made in the body of the protocol were also implemented in the Synopsis, where applicable.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title page	Revised Sponsor contact information.	To update clinical team members.
Section 2 (Schedule of Activities), Table 2-1 (Screening Period Procedural Outline)	Clarified that 100-mg aspirin dosing can start on Day 2 for participants who received at least 75 mg as standard of care on the same day as randomization.	To accommodate for regional or institutional practices regarding aspirin administration during acute management of stroke/TIA.
Section 2 (Schedule of Activities), Table 2-1 (Screening Period Procedural Outline)	Clarified that following a standard-of-care clopidogrel loading dose, the standard-of-care clopidogrel daily dose of 75 mg may be taken prior to randomization.	To accommodate for regional or institutional practices regarding clopidogrel administration during acute management of stroke/TIA.
Section 2 (Schedule of Activities), Table 2-1 (Screening Period Procedural Outline)	Added note: A clinical (standard-of-care) MRI scan can be used as the baseline MRI provided that the clinical MRI protocol and scanner have been pre-approved by the central imaging vendor. Removed note: Study-specific, pretreatment (Day 1) MRI must be performed within 48 hours of the onset of the index event and prior to randomization.	To clarify conditions when it is acceptable to utilize a standard-of-care MRI protocol as the baseline MRI. The timing of the baseline MRI relative to the onset of the index event and randomization is outlined in the study-specific MRI row on Table 2-2.
Section 2 (Schedule of Activities), Table 2-1 (Screening Period Procedural Outline)	Specified the anatomical location where complete occlusion of a cervical carotid or an intracranial artery will require exclusion (proximal to the index lesion).	To clarify the required evidence for exclusion of participants with complete occlusion of a cervical carotid or an intracranial artery.
Section 2 (Schedule of Activities), Table 2-1 (Screening Period Procedural Outline)	Updated the notes to include a list of screening laboratory tests that are required be performed locally to assess eligibility.	To provide clarification to sites as to what screening labs need to be performed locally to assess eligibility.
Section 2 (Schedule of Activities), Table 2-1 (Screening Period Procedural Outline)	Modified required duration of SAE collection from 7 days after discontinuation of dosing to through the follow-up period.	To enable SAE collection through the follow-up period for participants who discontinue study treatment early and align with post-randomization NSAE collection.
Section 2 (Schedule of Activities), Table 2-1 (Screening Period Procedural Outline)	Added guidance as to where results of local labs performed for assessment of SAEs should be sent.	To provide clarification to sites as to where results of local labs performed for assessment of SAEs should be sent.
Section 2 (Schedule of Activities), Table 2-2	Updated “brief physical examination” to “brief physical assessment.”	To enable performance of the physical assessment by delegated non-physician study staff on Day 21.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
(Post-Screening Period Procedural Outline)		
Section 2 (Schedule of Activities), Table 2-2 (Post-Screening Period Procedural Outline)	Provided instruction regarding instances where the baseline MRI cannot be performed within 48 hours of the index event and before randomization. Removed study-specific MRI sequences and referenced that sequences will be defined in imaging manual.	To enable flexibility without delaying randomization. The required MRI sequences are defined in the imaging manual.
Section 2 (Schedule of Activities), Table 2-2 (Post-Screening Period Procedural Outline)	Added instruction regarding performance of the Day 90 MRI when impacted by the COVID-19 pandemic.	To enable flexibility and preserve collection of the Day 90 MRI when impacted by the COVID-19 pandemic.
Section 2 (Schedule of Activities), Table 2-2 (Post-Screening Period Procedural Outline)	Clarified that participants may not be taking study medication past Day 96.	To accurately reflect consideration of study medication supply relative to obtaining the Day 90 MRI.
Section 2 (Schedule of Activities), Table 2-2 (Post-Screening Period Procedural Outline)	Clarified that 100-mg aspirin dosing can start on Day 2 for participants who received at least 75 mg as standard of care on the same day as randomization.	To accommodate for regional or institutional practices regarding aspirin administration during acute management of stroke/TIA.
Section 2 (Schedule of Activities), Table 2-2 (Screening Period Procedural Outline)	Clarified that following a standard-of-care clopidogrel loading dose, the standard-of-care clopidogrel daily dose of 75 mg may be taken prior to randomization.	To accommodate for regional or institutional practices regarding clopidogrel administration during acute management of stroke/TIA.
Section 2 (Schedule of Activities), Table 2-2 (Post-Screening Period Procedural Outline)	NIHSS score for qualifying event was increased from ≤5 to ≤7.	The NIHSS score for qualifying event was increased based on review of aggregate safety data to date and Steering Committee feedback.
Section 2 (Schedule of Activities), Table 2-2 (Post-Screening Period Procedural Outline)	Updated the notes to include pregnancy requirements.	To provide clarity to the sites on the pregnancy testing expectations.
Section 2 (Schedule of Activities), Table 2-2 (Post-Screening Period Procedural Outline)	Modified required duration of SAE collection after discontinuation of dosing from 7 days to through the follow-up period.	To enable SAE collection through the follow-up period for participants who discontinue study treatment early and align with post-randomization NSAE collection.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2 (Schedule of Activities), Table 2-2 (Post-Screening Period Procedural Outline)	Added guidance as to where results of local labs performed for assessment of SAEs should be sent.	To provide clarification to sites as to where results of local labs performed for assessment of SAEs should be sent.
Section 2 (Schedule of Activities), Table 2-2 (Post-Screening Period Procedural Outline)	Provided instruction to clarify that the timing of first dose of study medication remains unchanged in instances when the baseline MRI is completed after 48 hours from the onset of the index event.	To reaffirm unchanged first dose requirements relative to onset of the index event even when study-specific MRI cannot be completed within 48 hours from the onset of the index event.
Section 2 (Schedule of Activities), Table 2-2 (Post-Screening Period Procedural Outline)	Modified table footnotes to reflect changes in the table and protocol body.	To accurately reflect protocol body content.
Section 3.2.1 (Phase 1 and 2a studies with BMS-986177), Table 3.2.1-1 (Highlights of Clinical Pharmacology)	Clarified that Tmax was in fasted state and that Accumulation Index was for QD dosing only.	To provide clarification on the conditions where the PK properties were determined.
Section 5.1 (Overall Design)	Removed ±10-day visit window and added instruction regarding performance of the Day 90 MRI when impacted by the COVID-19 pandemic.	To enable flexibility and preserve collection of Day 90 MRI when impacted by the COVID-19 pandemic.
Section 5.1 (Overall Design)	Updated enrollment period duration from 26 months to 36 months.	To reflect updated enrollment projections.
Section 5.1 (Overall Design, Screening Period)	Provided instruction regarding instances where the baseline MRI cannot be performed within 48 hours of the index event and before randomization.	To enable flexibility without delaying randomization.
Section 5.1 (Overall Design, Screening Period)	Specified the anatomical location for the assessment of complete occlusion of a cervical carotid or an intracranial artery (proximal to the index lesion).	To clarify the required evidence for exclusion of participants with complete occlusion of a cervical carotid or an intracranial artery.
Section 5.1 (Overall Design, Double-Blind Treatment Period)	Restructured order of activities to be performed during the double-blind treatment period.	To clarify the sequence of activities to be performed during the double-blind treatment period.
Section 5.1 (Overall Design, Double-Blind Treatment Period)	Added statement that the DMC recommendation regarding the Day 60 clinical laboratory sample will be communicated to the investigator by the Sponsor.	To provide clarity regarding communication of the DMC recommendation to the investigator without the need for a protocol amendment.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1 (Overall Design, Double-Blind Treatment Period, and Figure 5.1-1 Study Design Schematic)	Updated the milestone requirement for DMC review prior to decision on inclusion of the 200-mg BID dose arm.	In light of modifications to the inclusion/exclusion criteria, the DMC milestone requirements were updated to enable safety evaluation of study population prior to the inclusion of the 200-mg BID arm.
Section 5.1 (Overall Design, Double-Blind Treatment Period)	Clarified that following a standard-of-care clopidogrel loading dose, the standard-of-care clopidogrel daily dose of 75 mg may be taken prior to randomization.	To accommodate for regional or institutional practices regarding clopidogrel administration during acute management of stroke/TIA.
Section 5.1 (Overall Design, Double-Blind Treatment Period)	Clarified that 100-mg aspirin dosing can start on Day 2 for participants who received at least 75 mg as standard of care on the same day as randomization.	To accommodate for regional or institutional practices regarding aspirin administration during acute management of stroke/TIA.
Section 5.1 (Overall Design, Double-Blind Treatment Period)	Added statement that alternative measures can be considered to obtain required visit assessments for participants who are unable or not permitted to attend an onsite visit due to the COVID-19 pandemic as local regulatory requirements permit.	To preserve study assessment collection for participants who are unable or not permitted to attend an onsite visit due to the COVID-19 pandemic.
Section 5.1 (Overall Design, Double-Blind Treatment Period)	Updated Day 60 visit description to ease telephone contact requirement for participants who reviewed required assessments at Day 60 site visit and removed requirement of reviewing Day 60 clinical laboratory results with participant.	To provide flexibility to sites and participants who are able to conduct all required assessment at Day 60 site visit.
Section 5.1 (Overall Design, Double-Blind Treatment and Follow-Up Period)	Clarified when the Day 97 end-of-study follow-up phone visit should occur for participants not completing treatment or not obtaining the Day 90 MRI.	To provide clear instruction on the requirement of the Day 97 end-of-study follow-up phone visit.
Section 5.1 (Overall Design, Double-Blind Treatment Period)	Added statement encouraging sites to perform follow-up phone call 7 days after permanent discontinuation.	To encourage follow-up contact is made with participants who permanently discontinue study medication.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1.1 (Data Monitoring and Other External Committees)	Updated the milestone requirements for DMC review prior to decision on inclusion of the 200-mg BID dose arm.	In light of modifications to the inclusion/exclusion criteria, the DMC milestone requirements were updated to enable safety evaluation of study population prior to the inclusion of the 200-mg BID arm.
Section 5.1.1 (Data Monitoring and Other External Committees)	Added statement that the DMC recommendation regarding the Day 60 clinical laboratory sample will be communicated to the investigator by the Sponsor.	To provide clarity regarding communication of the DMC recommendation to the investigator without the need for a protocol amendment.
Section 5.1.1 (Data Monitoring and Other External Committees)	Removed statement: "Recommendations for criteria to stop the clinical trial for safety concerns will be defined in the DMC charter." Added statement: "The DMC will use their clinical and statistical judgment to evaluate pertinent trial data and may recommend early termination of an individual study arm or the entire trial for important safety concerns that are felt to outweigh potential benefits. Details of the DMC activities will be described in a DMC charter.	To clarify that the Sponsor will not provide trial stopping criteria because the independent DMC is tasked to evaluate if the trial should be terminated early based on their clinical judgement of benefit-risk.
Section 6.1 (Inclusion Criteria)	NIHSS score for qualifying event was increased from ≤5 to ≤7.	The NIHSS score for qualifying event was increased based on review of aggregate safety data to date and feedback from Steering Committee.
Section 6.1 (Inclusion Criteria)	Specified the anatomical location where complete occlusion of a cervical carotid or an intracranial artery will require exclusion (proximal to the index lesion).	To clarify the required evidence for exclusion of participants with complete occlusion of a cervical carotid or an intracranial artery.
Section 6.1 (Inclusion Criteria)	Removed language regarding performance of baseline MRI within 48 hours of index event and prior to randomization and added statement that baseline MRI is required in this study in line with Section 9.2.12.	To reflect baseline MRI requirements in line with Section 9.2.12.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.1 (Inclusion Criteria)	Permitted the use of thrombolytic therapy/mechanical thrombectomy for treatment of the index event under specified conditions.	Based on aggregate safety data to date and feedback from Steering Committee, thrombolytic therapy/mechanical thrombectomy are now permitted provided that specified conditions are met in order to study a broader population that is closer to clinical practice.
Section 6.2 (Exclusion Criteria)	Added intracranial artery stenosis requiring angioplasty within 90 days to the exclusion criteria.	To clarify exclusion criteria regarding planned vascular treatment of intracranial artery stenosis.
Section 6.2 (Exclusion Criteria)	Removed use of thrombolytic therapy/mechanical thrombectomy from exclusion criteria.	Based on aggregate safety data to date and feedback from Steering Committee, thrombolytic therapy/mechanical thrombectomy are now permitted provided that specified conditions are met in order to study a broader population that is closer to clinical practice.
Section 6.2 (Exclusion Criteria)	Clarified that treated aneurysms without history of intracranial bleed are permitted.	To allow for enrollment of participants who present with treated aneurysms without history of intracranial bleed.
Section 6.2 (Exclusion Criteria)	Clarified UFH or LMWH for DVT prophylaxis allowance prior to enrollment.	To provide clear instruction on UFH or LMWH for DVT prophylaxis allowance prior to enrollment.
Section 6.2 (Exclusion Criteria)	Updated classification of strong CYP3A4/P-gp inhibitors and strong CYP3A4/P-gp inducers to combined P-gp and strong CYP3A4 inhibitors and combined P-gp and strong CYP3A4 inducers, respectively.	To reflect current classification of compounds with combined P-gp and CYP3A modulation properties.
Section 6.2 (Exclusion Criteria)	Updated INR exclusion requirement from INR >1.7 to INR >1.5.	The INR threshold was lowered for the safety of the study population that may receive thrombolytic therapy prior to randomization while also aligning laboratory exclusion requirements for all study participants.
Section 6.2 (Exclusion Criteria)	Updated criteria to include history of 12-lead ECG findings requiring exclusion.	Added clarification to also exclude participants with a history of ECG abnormalities as these participants have an increased risk for detection of an ECG finding during the study which may prompt early drug discontinuation.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2 (Exclusion Criteria)	Addition of SARS-CoV-2 infection within 4 weeks of screening and associated conditions regarding symptom resolution, investigator assessment, and consultation with Medical Monitor/Clinical Trial Physician.	To ensure safety of study participants and site personnel.
Section 7.2 (Method of Treatment Assignment)	Updated the milestone requirement for DMC review prior to decision on inclusion of the 200-mg BID dose arm.	In light of modifications to the inclusion/exclusion criteria, the DMC milestone requirements were updated to enable safety evaluation of study population prior to the inclusion of the 200-mg BID arm.
Section 7.3 (Selection and Timing of Dose for Each Participant)	Clarified that following a standard-of-care clopidogrel loading dose, the standard-of-care clopidogrel daily dose of 75 mg may be taken prior to randomization.	To accommodate for regional or institutional practices regarding clopidogrel administration during acute management of stroke/TIA.
Section 7.3 (Selection and Timing of Dose for Each Participant)	Restructured language regarding clopidogrel loading dose instructions.	To clarify 3 scenarios for administration of the clopidogrel loading dose.
Section 7.3 (Selection and Timing of Dose for Each Participant)	Clarified that 100-mg aspirin dosing can start on Day 2 for participants who received at least 75 mg as standard of care on the same day as randomization.	To accommodate for regional or institutional practices regarding aspirin administration during acute management of stroke/TIA.
Section 7.3 (Selection and Timing of Dose for Each Participant)	Provided instruction to clarify that the timing of first dose of study medication remains unchanged in instances when the baseline MRI is completed after 48 hours from the onset of the index event.	To reaffirm unchanged first dose requirements relative to onset of the index event even when baseline MRI cannot be completed within 48 hours from the onset of the index event.
Section 7.3 (Selection and Timing of Dose for Each Participant)	Updated study medication duration of resupply on Day 21 from 70 days to 64 days.	To accurately reflect the study medication re-supply that participant is receiving.
Section 7.3 (Selection and Timing of Dose for Each Participant)	Updated the consideration that participant may not be taking study medication past Day 96 when Day 90 MRI is performed past ± 6-day window due to the COVID-19 pandemic.	To accurately reflect consideration of study medication supply relative to obtaining Day 90 MRI when impacted by the COVID-19 pandemic.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.4 (Blinding)	Clarified that designated staff of Bristol-Myers Squibb Research & Development not involved in the study will provide assistance for analyses needed for DMC in scope of the DMC charter.	To provide clarification on unblinding of designated Bristol-Myers Squibb staff not involved in the study who are performing analyses needed for DMC in scope of the DMC charter.
Section 7.7.1 (Prohibited and/or Restricted Treatments)	Included all prohibited treatments from exclusion criteria.	To provide clarity on the prohibited treatments from exclusion criteria instead of referencing the section.
Section 7.7.2.1 (Imaging Restrictions and Precautions)	Updated contrast restriction to allow for contrast administration as per investigator discretion and local clinical practice.	To accommodate for regional or institutional practices regarding contrast administration for MRIs.
Section 8.4 (Emergency Procedures)	Removed statement that study drug BMS-986177 must be discontinued if thrombolytic therapy or thrombectomy is used. Added statement that study drug BMS-986177 must be interrupted after thrombolytic therapy or thrombectomy and specified conditions that need to be met to permit re-start.	Based on aggregate safety data and feedback from the Steering Committee, study drug BMS-986177 must be interrupted and can be restarted if thrombolytic therapy is administered or thrombectomy is performed provided that specified conditions are all met.
Section 8.5 (Other Reasons for Permanent Discontinuation from Study Treatment)	Removed statement that study drug BMS-986177 must be permanently discontinued if thrombolytic therapy or thrombectomy is used.	Based on aggregate safety data and feedback from the Steering Committee, study drug BMS-986177 can be restarted if thrombolytic therapy or thrombectomy were used during the treatment period, provided that all specified conditions are met.
Section 8.6 (Discontinuation from Study)	Clarified the Day 90 and Day 97 visit assessment requirements if end-of-treatment visit is completed.	To provide clear instruction to sites regarding participants who discontinue early and complete end-of-treatment visit requirements. Specifically, that for these participants only the Day 90 MRI is required on the Day 90 visit and that the Day 97 visit should be completed.
Section 8.6 (Discontinuation from Study)	Added statement encouraging sites to perform follow-up phone call 7 days after permanent discontinuation.	To encourage follow-up contact is made with participants who permanently discontinue study medication.
Section 8.6 (Discontinuation from Study)	Clarified conditions when Day 97 end-of-study follow-up phone visit should occur.	To provide clear instruction on requirement of Day 97 end-of-study follow-up phone visit.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.7 (Post-Study Treatment Follow-up)	Added instruction regarding performance of the Day 90 MRI when impacted by the COVID-19 pandemic.	To enable flexibility and preserve collection of Day 90 MRI when impacted by the COVID-19 pandemic.
Section 9.1 (Efficacy Assessments)	Provided instruction regarding instances where the baseline MRI cannot be performed within 48 hours of the index event and before randomization.	To enable flexibility without delaying randomization.
Section 9.1 (Efficacy Assessments)	Provided instruction to clarify that the timing of first dose of study medication remains unchanged in instances when the baseline MRI is completed after 48 hours from the onset of the index event.	To reaffirm unchanged first dose requirements relative to onset of the index event even when baseline MRI cannot be completed within 48 hours from the onset of the index event.
Section 9.2.3 (Time Period and Frequency for Collecting AE and SAE information)	Clarified that nonserious AE collection should begin at randomization.	To align with adverse event reporting in Table 2-2 (Post-Screening Procedural Outline).
Section 9.2.3 (Time Period and Frequency for Collecting AE and SAE information)	Modified required duration of SAE collection after discontinuation of dosing from 7 days to through the follow-up period.	To enable SAE collection through the follow-up period for participants who discontinue study treatment early and align with post-randomization NSAE collection.
Section 9.2.3 (Time Period and Frequency for Collecting AE and SAE information)	Added guidance as to where results of local labs performed for assessment of SAEs should be sent.	To provide clarification to sites as to where results of local labs performed for assessment of SAEs should be sent.
Section 9.2.12 (Magnetic Resonance Imaging)	Clarified that a clinical (standard-of-care) MRI scan can be used as the baseline MRI provided that the clinical MRI protocol and scanner have been pre-approved by the central imaging vendor.	To clarify conditions when it is acceptable to utilize a standard-of-care MRI protocol as the baseline MRI.
Section 9.2.12 (Magnetic Resonance Imaging)	Provided instruction regarding instances where the baseline MRI cannot be performed within 48 hours of the index event and before randomization.	To enable flexibility without delaying randomization.
Section 9.2.12 (Magnetic Resonance Imaging)	Removed ±10-day window and added instruction regarding performance of the Day 90 MRI when impacted by the COVID-19 pandemic.	To enable flexibility and preserve collection of Day 90 MRI when impacted by the COVID-19 pandemic.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.2.12 (Magnetic Resonance Imaging)	Updated the consideration that participant may not be taking study medication past Day 96 when Day 90 MRI is performed past ± 6-day window due to the COVID-19 pandemic.	To accurately reflect consideration of study medication supply relative to obtaining Day 90 MRI when impacted by the COVID-19 pandemic.
Section 9.2.12 (Magnetic Resonance Imaging)	Restructured language for clarity.	To provide clear guidance on MRI requirements for investigators.
Section 9.2.13 Physical Examinations	Updated "brief physical examination" to "brief physical assessment."	To enable performance of the physical assessment by delegated non-physician study staff on Day 21.
Section 9.3 (PK, PD, Biomarkers and PK/PD Assessments), Table 9.3.1.1-1 (Pharmacokinetic Sampling Schedule)	Simplified pharmacokinetic sampling schedule.	To enable flexibility to sites for PK sampling based on feedback from investigators.
Section 9.3 (PK, PD, Biomarkers and PK/PD Assessments), Section 9.3.2.1 (Exploratory Biomarker Assessments)	Added biomarkers related to SARS-CoV-2 infection status or related pathophysiological pathways.	SARS-CoV-2 serologic status may help advance the understanding of the impact of SARS-CoV-2 on BMS-986177 and cardiovascular disease.
Section 9.3 (PK, PD, Biomarkers and PK/PD Assessments), Table 9.3.2.1-1 (Biomarker sampling Schedule)	Simplified biomarker sampling schedule.	To enable flexibility to sites for biomarker sampling based on feedback from investigators.
Section 9.4 (Other Assessments), Section 9.4.1 (Assessment of Index Stroke and New Strokes)	NIHSS score for qualifying event was increased from ≤5 to ≤7.	The NIHSS score for qualifying event was increased based on review of aggregate safety data to date and feedback from Steering Committee.
Section 10.1 (Sample Size Determination)	Provided sample size estimations for the study without inclusion of the 200-mg BID dose arm.	To provide an additional statistical sample size determination in case the 200-mg BID dose arm is not included in the randomization scheme.
Appendix 2 (Study Governance Considerations)	Added statement to specify that other means of remote monitoring approved by the Sponsor and as local regulatory requirements permit can be considered.	To clarify conditions where remote monitoring can be considered.
Appendix 11 (Strong CYP3A inhibitor list)	Updated classification in title and body to combined P-gp and strong CYP3A4 inhibitors.	To reflect current classification of compounds with combined P-gp and CYP3A modulation properties.
Appendix 12 (Strong CYP3A inducer list)	Updated classification in title and body to combined P-gp and strong CYP3A4 inducers.	To reflect current classification of compounds with combined P-gp and CYP3A modulation properties.

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1 SYNOPSIS

Protocol Title:

A Global, Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of BMS-986177, an Oral Factor XIa Inhibitor, for the Prevention of New Ischemic Stroke or New Covert Brain Infarction in Patients Receiving Aspirin and Clopidogrel Following Acute Ischemic Stroke or Transient Ischemic Attack (TIA)

AXIOMATIC-SSP: Antithrombotic Treatment with Factor **XI**a Inhibition to **O**ptimize **M**anagement of **A**cute **T**hromboembol**ic** Events in **S**econdary **S**troke **P**revention

Study Phase:

2

Rationale:

Bleeding, especially intracranial hemorrhage (ICH), is the major concern among clinicians when considering antithrombotic therapy in patients with stroke and threatened stroke. A major advance of the past decade in anticoagulation has been the introduction of selective oral direct thrombin and Factor Xa inhibitors (DOACs). The risk of ICH with DOACs is sharply reduced compared with warfarin.

BMS-986177 (also known as JNJ-70033093) is a small molecule that binds and inhibits the activated form of human coagulation Factor XI (Factor XIa) with high affinity and selectivity. According to the scientific evidence accumulated to date, the inhibition of FXI may provide a novel mechanism for systemic antithrombotic effects without increasing the risk of clinically significant bleeding in a variety of conditions predisposing to high risk of thrombotic events.

The rationale for this study is that Factor XIa inhibition has the potential to reduce thrombin generation enough to prevent vascular occlusion and embolism without impairing hemostasis. The following observations support this concept: (1) the highest levels of Factor XI activity are associated with a heightened risk of ischemic stroke; (2) lower levels of Factor XI activity are associated with a reduced risk of ischemic stroke; (3) Factor XI deficiency is rarely associated with unprovoked major bleeding; (4) although not done in participants with stroke, a Phase 2 study for VTE prophylaxis in participants post total knee replacement with another Factor XIa inhibitor provides a proof-of-concept. The study showed that reducing FXI levels to 20% or less than normal with an antisense inhibitor of FXI synthesis reduced the risk of postoperative VTE compared to enoxaparin, without an increase in bleeding compared to enoxaparin.

The recently-reported POINT and CHANCE studies demonstrated that treatment with aspirin and clopidogrel is more effective than aspirin alone in reducing the risk of recurrent stroke. However, the residual risk for recurrent stroke remains high, even when patients are treated with combination of aspirin and clopidogrel, emphasizes the continuing need for a more effective therapeutic option. Two possible strategies for achieving better efficacy are more potent antiplatelet therapy or dual pathway inhibition of thrombus formation.

BMS-986177 combined with antiplatelet therapy has the potential to be safe and more effective than antiplatelet therapy alone. A recently completed drug-drug interaction (DDI) study in healthy volunteers was conducted to assess the safety and tolerability of multiple-dose BMS-986177 200 mg given twice daily (BID) for 5 days with and without dual antiplatelet therapy. Clopidogrel was given as 300 mg on Day 1 followed by 4 days of 75 mg clopidogrel, and aspirin 325 mg was administered once daily [QD] for 5 days. There were no serious bleeding events reported from any of the 113 healthy participants, including 37 participants treated with DAPT + BMS-986177, in the DDI study. There were a few minor bleeding events, which showed no trend toward any treatment group. These preliminary findings are consistent with the notion that FXIa inhibition is associated with a low risk of bleeding, and support the proposed clinical trial with BMS-986177, aspirin and clopidogrel.

Finally, the rationale for treating all patients with aspirin + clopidogrel is based on the lack of credible clinical trial data to support a net clinical benefit of anticoagulation alone over antiplatelet therapy for secondary prevention of non-cardioembolic strokes. As noted above, this situation is reflected in guidelines recommending antiplatelet therapy for secondary stroke prevention in this population. The data summarized above support the hypothesis that inhibition of Factor XIa could be a promising target for antithrombotic therapy for stroke, potentially providing sufficient inhibition of thrombin generation to prevent thrombotic vascular occlusion or embolization without impairing hemostasis.

Study Population:

Approximately and up to 2350 participants, ≥ 40 years of age, identified within 48 hours of onset of signs and/or symptoms of stroke or TIA will be included in this study.

Key Inclusion Criteria:

Type of Participant and Target Disease Characteristics

- **Ischemic stroke:** a neurological deficit attributable to a non-lacunar, acute brain infarction detected by neuroimaging (CT or MRI) and relevant to the clinical symptoms.

  AND

  National Institutes of Health Stroke Score (NIHSS) ≤ 7 at time of randomization

  AND

  Evidence of relevant intracranial or cervical arterial atherosclerotic plaque, ulceration or thrombus in a feeding artery documented by imaging (either Doppler ultrasound or CTA or MRA or catheter angiography)

  ***Note**:* Atherosclerotic plaque does not need to be severe or stenotic, but must be visible. Participants with complete occlusion of a cervical carotid or intracranial artery that is proximal to the index lesion should be excluded.

  AND

  Modified Rankin Score (mRS) ≤ 3 before the index event (pre-morbid)

- **TIA**: acute onset neurological deficit attributable to focal ischemia of the brain by history or examination, with complete resolution of the deficit and no brain infarction on neuroimaging (CT or MRI)

  AND

  ABCD2 SCORE ≥6 or motor symptoms

  AND

  Evidence of relevant intracranial or cervical arterial atherosclerotic plaque, ulceration or thrombus in a feeding artery documented by imaging (either Doppler ultrasound or CTA or MRA or catheter angiography)

  ***Note**:* Atherosclerotic plaque does not need to be severe or stenotic, but must be visible. Participants with complete occlusion of a cervical carotid or intracranial artery that is proximal to the index lesion should be excluded.

  AND

  Modified Rankin Score (mRS) ≤3 before the index event (pre-morbid)

- Two MRI scans are required for participation in this study. Therefore, participants must have a body habitus suitable for MRI and cannot have any contraindications to the performance of the MRI. (eg, weight limit, MRI-incompatible implanted devices, infusion pump that cannot be discontinued temporarily for the scan).
- No contraindication to clopidogrel or aspirin and suitable for treatment with aspirin 100 mg per day for at least 90 days.
- Enrollment of subjects who have received thrombolytic therapy or mechanical thrombectomy (without stenting) for the treatment of the index event is permitted if all of the following conditions are met:
  - At least 24 hours have elapsed between end of IV thrombolytic use/thrombectomy and first dose of study medication.
  - Neuroimaging (either clinical imaging or study MRI) after IV thrombolytic therapy/ post-thrombectomy excludes any hemorrhagic transformation.
  - NIHSS ≤ 7 at time of randomization.
  - Post-thrombolytic therapy/post-thrombectomy INR ≤ 1.5, aPTT ≤ 1.4 prior to study treatment administration.
  - No contraindications have been identified that in the opinion of the investigator would preclude start of study medication (eg, large infarct volume, procedure-related bleeding).
  - All other study criteria are met.

In addition, we recommend following local practice and considering fibrinogen > 150 mg/dL before initiation of study treatment.

Key Exclusion Criteria:

- Predicted inability to swallow study medication
- Women who are pregnant or breastfeeding
- Any condition that, in the opinion of the investigator, contraindicates anticoagulant therapy or would have an unacceptable risk of bleeding such as a large infarct volume (per investigator discretion) or uncontrolled hypertension.
- Hemorrhage, tumor, arteritis, large vessel dissection, arteriovenous malformation (AVM), or other pathology that could account for index symptoms must be excluded by CT or MRI interpreted locally.
- Symptomatic carotid stenosis or intracranial artery stenosis for which endarterectomy or angioplasty is planned within 90 days.
- Any condition for which chronic anticoagulation is indicated and expected to be initiated (eg, NVAF, DVT, PE)
- Requirement for continued use of dual antiplatelet therapy (DAPT) for more than 21 days or non-aspirin antiplatelet therapy or anticoagulant for another medical condition (eg, prophylaxis for venous thromboembolism).

  Note: Treatment with clopidogrel, aspirin, dipyridamole or another P2Y12 inhibitor prior to enrollment is allowed. Treatment with aspirin at a different dose before enrollment is also allowed. All participants must transition to the protocol-defined treatments and doses at randomization. No clopidogrel loading dose is needed for participants who received a clopidogrel loading dose prior to randomization. Participants who report taking chronic clopidogrel also require a 300-mg clopidogrel loading dose unless the investigator can verify that the participant has taken the daily dose for at least the preceding 3 days. Participants who have received dipyridamole or another P2Y12 inhibitor must receive the clopidogrel loading dose after discontinuing the non-clopidogrel P2Y12 inhibitor or dipyridamole/dipyridamole-containing treatment.
- History of hemorrhage into the brain, subarachnoid hemorrhage, subdural hematoma or spinal cord hemorrhage except cerebral microbleeds (CMB) and minor hemorrhagic transformation of prior infarct manifesting as scattered petechiae (Hemorrhagic Infarction Type 1 [HI1] according to Heidelberg classification).

  Note: CMBs are defined as rounded foci of $\leq$10 mm in size that appear hypointense and distinct from vascular flow voids, leptomeningeal hemosiderosis, or non-hemorrhagic subcortical mineralization on T2* weighted MRI.
- History of clinically meaningful hepatic disease and/or clinically significant abnormal liver function.
- Any of the following laboratory results outside of the ranges specified below prior to study treatment administration, confirmed by repeat:
  - Hemoglobin <9 g/dL
  - Platelet count <100,000 mm3
  - aPTT >1.4x upper limit of normal (ULN)
  - INR >1.5
  - AST or ALT >3x ULN

- Intracranial tumor (except meningioma, which is permitted) or aneurysm >5 mm or AVM (except treated aneurysm without history of intracranial bleed, which is permitted.)
- History of end-stage renal disease (ESRD) with eGFR <15 mL/min/1.73m^2, or requiring dialysis
- Planned use of anticoagulants including warfarin or other vitamin K antagonists, oral thrombin and Factor Xa inhibitors, bivalirudin, hirudin, argatroban, unfractionated and low molecular weight heparins, with the exception of heparin or low molecular weight heparin (LMWH) used to maintain patency of indwelling catheters.

  Note: Participants who received UFH or LMWH for DVT prophylaxis prior to randomization can be enrolled. The use of anticoagulants for post-stroke DVT prophylaxis after randomization is prohibited. For post-stroke DVT prophylaxis, non-pharmacological prophylaxis (i.e. intermittent pneumatic compression) is recommended.
- Anticipated concomitant chronic (>14 days) use of systemic nonsteroidal anti-inflammatory drugs (NSAIDs). NSAID (including COX-2 inhibitors) use prior to randomization is allowed.
- Use of combined P-glycoprotein (P-gp) and strong CYP3A4 inhibitors or combined P-gp and strong CYP3A4 inducers in the 7 days prior to randomization, or the need for ongoing treatment with concomitant oral or intravenous therapy with combined P-gp and strong CYP3A4 inhibitors or combined P-gp and strong CYP3A4 inducers during the study. A list of combined P-gp and strong CYP3A4 inhibitors is attached as Appendix 11. A list of combined P-gp and strong CYP3A4 inducers is attached as Appendix 12.
- Planned concomitant use of omeprazole or esomeprazole after randomization for the duration of clopidogrel treatment (eg, H2 blockers [except cimetidine] and other PPIs are allowed).
- History of or any of the following findings on 12-lead ECG prior to study drug administration: atrial fibrillation, atrial flutter, complete heart block, or Mobitz 2 second-degree heart block.
- Known SARS-CoV-2 infection within 4 weeks prior to screening.

  Note: To be considered for enrollment, symptoms must have completely resolved and based on investigator assessment in consultation with the Medical Monitor/Clinical Trial Physician, and there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.

The following table outlines the objectives and endpoints for the study. Definitions and details related to study endpoints can be found in the Study Events Assessment Manual.

Objective	**Endpoints**
Primary	
To estimate the dose-response relationship of BMS-986177 in participants with ischemic stroke or TIA treated with aspirin and clopidogrel	Composite of new ischemic stroke during the treatment period and new covert brain infarction (FLAIR + DWI) detected by MRI at Day 90 (MRI assessed by central review)

Objective	Endpoints
Secondary	
To assess the rate of major bleeding after treatment with BMS-986177 relative to placebo	Event rate based on bleeding according to Bleeding Academic Research Consortium (BARC) Type 3 and 5
To assess the rate of all bleeding after treatment with BMS-986177 relative to placebo	Event rate based on BARC, ISTH and PLATO-defined criteria
To compare the rate of the composite of new ischemic stroke and new covert brain infarction detected by MRI at Day 90 during treatment with BMS-986177 compared to placebo	Rate of the composite of new ischemic stroke during the treatment period and new covert brain infarction (FLAIR + DWI) detected by MRI at 90 days
To assess the effect of BMS-986177 on characteristics of brain lesions on Day 90 MRI	Location, number, and volume of new FLAIR + DWI lesions
To compare the rate of the composite of new ischemic stroke, myocardial infarction (MI) and all-cause mortality during treatment with BMS-986177 *vs.* placebo	Event rates for new ischemic, non-fatal stroke, non-fatal MI, and all-cause death during the treatment period
To assess stroke severity, neurological, and cognitive function following BMS-986177 treatment *vs.* placebo	National Institutes of Health Stroke Scale (NIHSS), Modified Rankin Scale (mRS), Montreal Cognitive Assessment (MoCA), and Digit Symbol Substitution Test (subtest of WAIS-IV) at baseline, on Days 21 and 90, and at the time of a new stroke event
To assess the safety and tolerability of BMS-986177	Adverse events, vital signs, physical exams, electrocardiogram (ECG) and clinical laboratory results
To assess the pharmacokinetics (PK) of BMS-986177 and potential effects of covariates on exposure	Estimated clearance (CL) and volume of distribution (Vd) and effect of body weight, age, gender, race, renal function, liver function, concomitant medications
To assess the dose-response of BMS-986177 on pharmacodynamic (PD) biomarkers	% change from baseline in aPTT and Factor XI clotting activity during treatment
Exploratory	
To assess the effect of BMS-986177 on characteristics of cerebral microbleeds (CMBs), hemorrhagic transformation of ischemic stroke and asymptomatic intracranial bleeding on Day 90 MRI	Incidence and characteristics of CMBs, hemorrhagic transformation of ischemic stroke and asymptomatic intracranial bleeding on Day 90 MRI
To explore the exposure-response (E-R) relationship of BMS-986177 on efficacy endpoints	New ischemic, non-fatal stroke, non-fatal MI, and all-cause death during the treatment period
To explore the E-R relationship of BMS-986177 on major bleeding	Bleeding according to BARC Type 3 and 5 definitions
To assess the PK of clopidogrel (and metabolites), aspirin and salicylic acid	Clopidogrel (and metabolites), aspirin and salicylic acid plasma concentrations
To explore the E-R relationship of BMS-986177 on aPTT and Factor XI clotting activity	Change from baseline in aPTT and Factor XI clotting activity during treatment
To explore biomarkers related to FXI pathway, stroke, thrombosis/hemostasis, inflammation and cardiovascular diseases, and their relationship to BMS-986177 treatment and selected endpoints	These markers may include, but are not limited to: plasma D-dimer, PT, F1.2, and Factor XI antigen.

Overall Design:

The study is a multi-center, Phase 2, randomized, double-blind, placebo-controlled, dose-ranging trial. Eligible participants will be screened for potential inclusion into the study as soon as possible after presentation and randomized within 48 hours of the index event.

Following signing of informed consent, participants will be randomized to receive BMS-986177 or placebo, plus open-label uncoated aspirin 100 mg in combination with clopidogrel (a loading dose followed by maintenance doses) for the next 21 days. Participants will continue treatment from Day 22 through Day 90 with BMS-986177 or placebo, plus open-label 100-mg uncoated aspirin only.

Aspirin and clopidogrel will be given open-label as a background therapy according to the following scenarios:

1) Prior to signing informed consent:
   - Participants who have received a single open-label clopidogrel loading dose of between 300 mg and 600 mg as standard-of-care prior to obtaining informed consent can be enrolled in the study. No additional loading dose of clopidogrel is required for such participants after randomization.
   - Following a standard-of-care clopidogrel loading dose, the standard-of-care clopidogrel daily dose of 75 mg will be taken the next day, and it can be taken prior to randomization.
   - Participants who report taking chronic clopidogrel also require a 300-mg clopidogrel loading dose unless the investigator can verify that the participant has taken the daily dose for at least the preceding 3 days.
2) Prior to randomization and after signing informed consent:
   - Following signing of informed consent, a 300-mg loading dose of clopidogrel and 100 mg aspirin may be assigned for immediate treatment upon consenting the participant and registering the participant in Interactive Response Technology (IRT), if considered clinically appropriate. Daily 75 mg clopidogrel and 100 mg daily aspirin will be started the next day.
3) After randomization:
   - A clopidogrel loading dose of 300 mg along with 100 mg aspirin will be administered after randomization on Day 1 for participants who have not received any clopidogrel loading dose.

For participants who have received at least 75 mg aspirin as standard of care before randomization, and if this dose was taken on the same day as randomization, then no additional aspirin is required on Day 1. In this case, 100 mg daily aspirin should be started in the morning of Day 2.

A baseline MRI will be performed within 48 hours of the onset of the index event, and prior to randomization. The first dose of double-blind study medication (BMS-986177 or placebo) should be taken as soon as possible after the baseline MRI assessment, preferably within 2 hours, but no

longer than 6 hours. If outside of the 6-hour post-MRI window, the investigator should call the Medical Monitor for guidance. In instances where the baseline MRI is completed after 48 hours from the onset of the index event, the first dose of study medication should still be taken immediately after randomization and within 48 hours from the onset of the index event.

BMS-986177 or placebo will be taken twice daily (BID), once in the morning (between 6AM - 9AM) and again in the evening (between 6PM - 9PM).

An MRI of the brain will be performed on Day 90 ± 6 days (based on randomization on Day 1) All participants should remain on study treatment until the Day 90 MRI is performed up to Day 96.

Screening Period:

- All study assessments should occur within the first 48 hours of the index event, following participant consent.
- Within 48 hours of the onset of the index event, and prior to randomization, participants will have a baseline MRI (may be same as clinical MRI) whenever possible. If the baseline MRI cannot be performed within 48 hours of the index event and before randomization, it can be performed after randomization but must be performed within 72 hours of the index event and up to 24 hours after randomization. In instances where the baseline MRI is completed after 48 hours from the onset of the index event, the first dose of study medication should still be taken immediately after randomization within 48 hours from the onset of the index event.
- Within 48 hours of the onset of the index event, and prior to randomization, all participants will have a Doppler ultrasound, CTA, MRA, or catheter angiography to assess for the presence of intracranial or cervical arterial atherosclerotic plaque, ulceration, or thrombus that is proximal to the index lesion. Use of available vascular imaging showing a qualifying lesion prior to the stroke event is allowed for participants who cannot complete the vascular imaging within 48 hours of the index event.
- At screening, the following will be obtained: physical examination, physical measurements, local clinical laboratory tests (including pregnancy test for WOCBP), vital signs, ECG, and medical history.
- The following functional/disease severity assessments are to be completed at screening: $ABCD^2$, NIHSS, mRS for eligibility assessment.

Double-blind Treatment Period:

- The double-blind treatment period will be from Day 1 to Day 90.
- During the initial phase of the study, a minimum of 800 participants will be randomized to one of the following 4 doses of BMS-986177: 25 mg daily (QD), 25 mg, 50 mg, or 100 mg twice daily (BID), or placebo. Twenty-five percent (25%) of the participants will be randomized to the placebo arm and the rest of participants will be randomized equally to the 4 doses of BMS-986177.

- All participants will be treated with open-label uncoated aspirin, 100 mg QD and clopidogrel, 75 mg QD (after a single 300 mg clopidogrel loading dose + aspirin 100 mg one day prior), for 21 days followed by aspirin alone from Day 22 to Day 90.
- On Day 1, prior to the initial dose of study medication, the following will be obtained: central clinical laboratory tests for safety, PD samples, exploratory biomarker samples, and optional pharmacogenomic samples.
- National Institutes of Health Stroke Score (NIHSS), Modified Rankin Scale (mRS), Montreal Cognitive Assessment (MoCA), and Digit Symbol Substitution Test (DSST; subtest of WAIS-IV) will be collected at baseline (at randomization for NIHSS), on Days 21 and 90, and at the time of a new stroke. MoCA and DSST (subset of WAIS-IV) will be read by a third-party central laboratory blinded to treatment.
- A Day 60 visit is required for central clinical safety laboratory sample within a ±7-day visit window for approximately 450 participants, after which the DMC will determine if such safety laboratory assessment will be continued, reduced, or discontinued. The DMC will review safety data, including clinical laboratory and any available imaging results when approximately 450 participants have completed the Day 21 visit. The DMC will recommend if further monitoring of Day 60 laboratory samples is needed. The DMC recommendation regarding the Day 60 clinical safety laboratory sample will be communicated to investigators by the study Sponsor.
- A telephone contact is required on Day 60 if all the respective assessments have not been completed onsite.
- Onsite visits will be required on Days 21 and 90 (end-of-treatment visit). At these visits, the following will be obtained: central laboratory tests for safety, PK, PD, and exploratory biomarkers.
- In the event participants are unable or not permitted to attend an onsite visit due to the COVID-19 pandemic, alternative measures can be considered to obtain required visit assessments as local regulatory requirements permit.
- The randomization of participants to the 200-mg BID dose may occur in a staggered approach after a minimum of 800 participants have been randomized. The decision to proceed with the 200-mg BID dose group will depend on the evaluation of the population, the DMC review of efficacy and safety data, and an assessment of whether it is safe to randomize participants to that dose group. When approximately 800 participants have been randomized, randomization for the placebo group will be used to achieve a 2:1 ratio relative to each treatment arm by the end of the study. Once a decision to add the 200-mg BID dose group has been made, randomization will be revised to achieve a target 2:1:1:1:1:1 (placebo: 25 mg QD: 25 mg BID: 50 mg BID: 100 mg BID: 200 mg BID) by the end of this study.
- All participants will also have an MRI assessment on Day 90 (±6 days) while continuing study drug treatment. In the event participants are unable or not permitted to attend the Day 90 visit due to the COVID-19 pandemic, the Day 90 MRI may be performed at a local facility provided that the study-specific MRI protocol is performed on a scanner pre-approved by the central imaging vendor. If the Day 90 MRI cannot be performed at a local facility, it may be performed when the participant is able or permitted to access the study site. For these participants, it is understood that they may not be taking study medication past Day 96.

- A telephone contact to assess efficacy and safety events will be required for all participants. For participants completing treatment, this contact will be timed within 7 days after the end of the treatment period and after the Day 90 MRI. For participants not completing treatment, an MRI is to be scheduled at Day 90, with a telephone contact scheduled 7 days after the Day 90 MRI; if for any reason a Day 90 MRI is not obtained, then a telephone contact is to be performed at Day 97 ± 2. Participants who permanently discontinue study treatment early should complete the end-of-treatment assessments, except MRI, at time of study drug discontinuation. For these participants, the Day 90 MRI as well as Day 97 visit must be completed at the planned visit days. Other Day 90 visit assessments do not need to be performed if they already were completed at the end-of-treatment visit. In addition, a follow-up telephone contact between discontinuation and Day 90 MRI is encouraged for participants who permanently discontinue study treatment early.
- For participants who withdraw consent for follow-up, there should be documentation of the reason for withdrawal. Study staff should explicitly seek information about the possible contribution of AEs to the participant's desire to withdraw and document any AEs that are identified in the AE section of the CRF.
- Early permanent discontinuation of study medication should be distinguished from withdrawal of consent for follow-up visits, telephone contacts, or medical records checks. Participants requesting withdrawal from the follow-up should be informed that withdrawal of consent for follow-up will result in loss of important information about the benefits and risks of BMS-986177.

Follow-up Period:

- To be discharged from the study, a telephone contact to assess efficacy and safety events will be required for all participants. For participants completing treatment, this contact will be timed within 7 days after the end of the treatment period and after the Day 90 MRI. For participants not completing treatment, an MRI is to be scheduled at Day 90, with a telephone contact scheduled 7 days after the Day 90 MRI. If for any reason a Day 90 MRI is not obtained, then a telephone contact is to be performed at Day 97 ± 2.

Number of Participants:

Approximately and up to 2350 participants from approximately 30 countries and approximately 380 clinical research sites will be randomized using a competitive enrollment approach.

Treatment Arms and Duration:

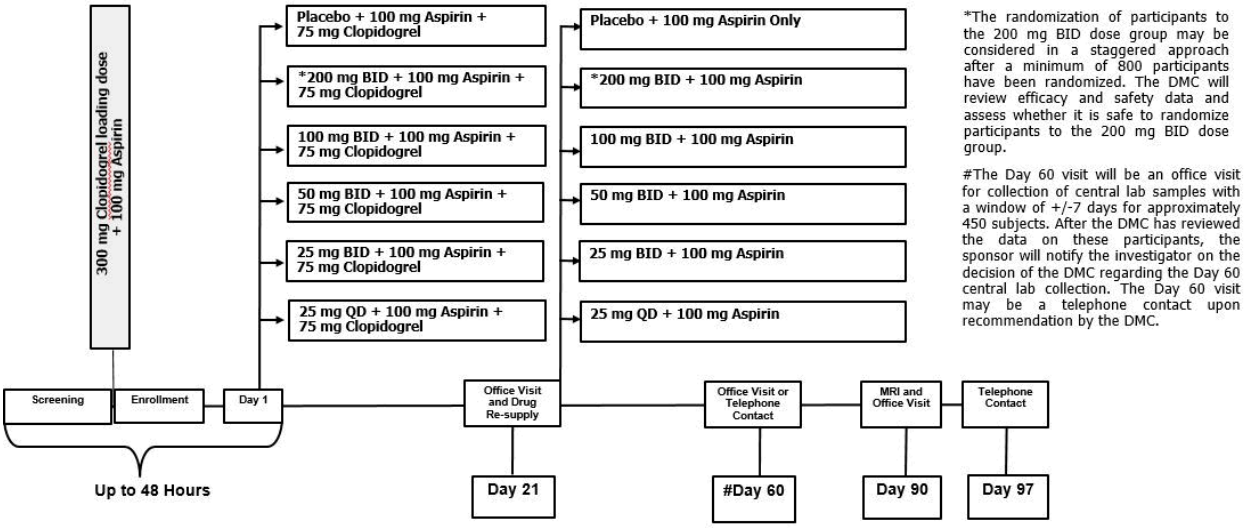
Study Drugs for CV010031

Medication	Dose Strength	IP/Non-IP
BMS-986177 Capsule	25 mg	IP
	100 mg	IP

Study Drugs for CV010031

Medication	Dose Strength	IP/Non-IP
Placebo For BMS-986177 Capsule	NA	IP
Clopidogrel Tablets	75 mg	IP
Uncoated Aspirin Tablets	100 mg	IP

Study Design Schematic:



The enrollment period for this trial will last approximately 36 months.

Data Monitoring Committee (DMC)

An independent DMC, whose activities will be described in a charter, will monitor the study. The DMC will be comprised of experienced clinicians, trialists and statistical experts. The DMC will review efficacy and safety data at designated times during the trial with the purpose of each review defined in the DMC charter. After approximately 450 participants have completed the Day 21 visit, the DMC will recommend if the Day 60 central laboratory samples are still needed. The DMC recommendation regarding the Day 60 clinical safety laboratory sample will be communicated to the investigator by the study Sponsor.

The DMC will review efficacy and safety data after a minimum of 800 participants have been randomized, and assess whether it is safe to randomize participants to the 200-mg BID dose group.

A list of drug discontinuation criteria for individual participants will be provided in the study protocol. Such criteria will include serious bleeding. The DMC will use their clinical and statistical judgment to evaluate pertinent trial data and may recommend early termination of an individual study arm or the entire trial for important safety concerns that are felt to outweigh potential benefits. Details of the DMC activities will be described in a DMC charter.

Steering Committee (SC)

The SC will consist of the Lead Investigator, who will serve as SC Chair. Other members will include: national leaders from other countries, other experts, and Sponsor representatives. The SC will be responsible for scientific aspects of the study and will ensure that the study execution and management are of the highest quality. The SC will convene regularly to discuss and report on ongoing supervision of the study.

Statistical Considerations

Sample Size: The primary endpoint for this study is the incidence of events within a composite of new ischemic stroke during the treatment period and new covert brain infarction (FLAIR + DWI) detected by MRI at 90 days. Sample size calculations were performed for detecting a dose-response effect with the MCP-MOD methodology using simulations with the Dose-Finding package in R statistical analysis software. Simulations of 2500 clinical trials were performed, assuming a true incidence for placebo of 15%, a plateau shaped dose response relationship with maximum relative risk reduction of 32% for BMS-986177 100 or 200 mg BID relative to placebo, and reductions of 10%, 17.5%, and 27% for the 25 mg QD, 25 mg BID, and 50 mg BID doses, respectively. Candidate models included an Emax model, a logistic model, and an exponential model.

Using these assumptions, a total of 2100 participants allocated in a 2:1:1:1:1:1 ratio to placebo and BMS-986177, 25-mg QD, 25-mg BID, 50-mg BID, 100-mg BID, and 200-mg BID groups provide approximately 80% power to demonstrate a dose-response relationship, with a 1-sided type I error of 0.049. Without the 200-mg group, a total of 1800 participants allocated in a 2:1:1:1:1 ratio to placebo and BMS 986177, 25-mg QD, 25-mg BID, 50-mg BID, and 100-mg BID groups would provide approximately 79% power to demonstrate a dose-response relationship with similar pattern, but risk reduction of 32% for BMS-986177 50- or 10-mg BID relative to placebo and reductions of 17.5%, and 27% for the 25-mg QD and 25-mg BID doses, respectively. Allowing up to 10% of participants who do not have a clinical event and also do not have a Day 90 imaging assessment, approximately and up to 2350 participants may be randomized. The frequency and reasons for missing data will be evaluated in blinded fashion during the course of the study.

Statistical Analyses: Dose-response relationship will be analyzed based on a generalized Multiple Comparisons and Modeling (gMCP-Mod) analysis for the BMS-986177 dose regimens, with placebo, and 25 mg QD as the lowest dose added to the ordered BID dose regimens. If a dose-response relationship exists, then fitted estimates for the incidence of the primary endpoint will be calculated in each of the treatment groups using the selected dose-response models. An Emax model, a logistic model, and an exponential model will be used as the candidate models for the gMCP-Mod analysis.

Point estimates with 95% confidence intervals for the following event rates will be summarized by treatment group.

- Composite of new ischemic stroke during the treatment period and new covert brain infarction detected by MRI at 90 days

- Composite of new ischemic non-fatal stroke, non-fatal MI, and all-cause mortality
- New ischemic stroke during the treatment period
- New covert brain infarction detected by MRI at Day 90
- All-cause death
- Non-fatal myocardial infarction (MI)

Dose-response analysis for new ischemic non-fatal stroke and the composite of new non-fatal stroke, non-fatal MI, and all-cause death will be assessed similar to the primary endpoint analysis.

Location, number, and volume of new FLAIR + DWI lesions will be summarized descriptively by treatment group.

Functional/disability/cognitive status assessed by the National Institutes of Health Stroke Score (NIHSS), modified Rankin Score (mRS), Montreal Cognitive Assessment (MoCA) and Digit Symbol Substitution Test (DSST; subtest of WAIS-IV) will be summarized by treatment group.

The event rates for all bleeding will be summarized by treatment group, including point estimates with 95% confidence intervals within group. Bleeding events will be summarized by BARC category, ISTH (major and CRNM bleeding), and PLATO criteria (major, including life-threatening and other; minor, and minimal).

Adverse events, vital signs, ECGs, and clinical laboratory results will be summarized by treatment group.

Except as otherwise noted, descriptive summaries will use data from all randomized groups, while dose-response analyses of primary and secondary endpoints will use data from participants randomized to placebo, 25 mg QD, and 25 mg, 50 mg, 100 mg, and 200 mg BID groups.

2 SCHEDULE OF ACTIVITIES

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

Table 2-1: Screening Period Procedural Outline (CV010031)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	Must be signed before any study procedures are initiated. See Appendix 2.
Participant Enrollment	X	Contact Interactive Response Technology (IRT) for participant number assignment and treatment assignment.
Inclusion/Exclusion Criteria	X	See Protocol Section 6.1 and 6.2.
Clopidogrel Loading Dose and Aspirin	X	Interactive web/voice response system (IRT) will dispense a 21-day supply of 75 mg clopidogrel and 100 mg aspirin, inclusive of the initial 300 mg clopidogrel loading dose and 100 mg aspirin. Upon consenting and registering participant in IRT, a 300 mg loading dose and 100 mg aspirin may be assigned for immediate treatment along with daily 75 mg clopidogrel and 100 mg daily aspirin, if considered clinically appropriate. For participants who have received at least 75 mg aspirin as standard of care before randomization, and if this dose was taken on the same day as randomization, then no additional aspirin is required on Day 1. In this case, 100 mg daily aspirin should be started in the morning of Day 2. Participants who have received a single loading dose of open-label clopidogrel between 300 mg to 600 mg as standard-of-care prior to obtaining informed consent can also be enrolled in the study. No additional loading dose of clopidogrel is required for such participants after randomization. Following a standard-of-care clopidogrel loading dose, the standard-of-care clopidogrel daily dose of 75 mg may be taken prior to randomization. Participants who report taking chronic clopidogrel also require a 300 mg clopidogrel loading dose unless the investigator can verify that the participant has taken the daily dose for at least the preceding 3 days.
Medical History	X	

Table 2-1: Screening Period Procedural Outline (CV010031)

Procedure	Screening Visit	Notes
Assessment of Signs and Symptoms		
Clinical MRI or CT for Exclusionary Pathology	X	Local assessment of magnetic resonance imaging (MRI) or computed tomography (CT) used to identify exclusionary pathology such as lacunar stroke, hemorrhage, arteriovenous malformation (AVM) or tumor. ***Note:*** A clinical (standard-of-care) MRI scan can be used as the baseline MRI provided that the clinical MRI protocol and scanner have been pre-approved by the central imaging vendor.[a]
Clinical Vascular Imaging	X	Doppler Ultrasound, CTA, MRA or Catheter Angiography to ascertain the presence of intracranial or cervical arterial atherosclerotic plaque, ulceration or thrombus in feeding artery. Use of available vascular imaging showing a qualifying lesion prior to the stroke event is allowed for participants who cannot complete the vascular imaging within 48 hours of the onset of the index event. • ***Note***: Atherosclerotic plaque does not need to be severe or stenotic, but must be visible. Participants with complete occlusion of a cervical carotid or an intracranial artery that is proximal to the index lesion should be excluded.
ABCD^2 for TIA	X	ABCD2 Score ≥6 or motor symptoms (see Section 9.4.2 and Appendix 6).
Modified Rankin Scale (mRS)	X	Pre-morbid mRS must be ≤3 (ie, before index event); to assess degree of disability or dependence in daily activities (see Section 9.4.3 and Appendix 7)
Full Physical Examination	X	See Protocol Section 9.2.13.
Physical Measurements	X	Height (screening only) and weight.
Vital Signs	X	Seated blood pressure and heart rate measured after the participant has been resting quietly for at least 5 minutes and before blood collection (see Section 9.2.14).
Concomitant Medication Use	X	All medications within 7 days prior to randomization (see Section 7.7).

Table 2-1: Screening Period Procedural Outline (CV010031)

Procedure	Screening Visit	Notes
Clinical Laboratory Tests	X	Screening clinical laboratory tests to assess eligibility, per inclusion/exclusion criteria, to be conducted locally and listed below (see Section 6 and Section 9.2.16). Laboratory samples collected as standard-of-care after the onset of the index event and prior to signing informed consent can be used to assess eligibility if meeting protocol-specified requirements. Results from the screening labs should be faxed or scanned and emailed to [redacted]. The following screening laboratory tests should be performed locally to assess eligibility and review should be documented prior to randomization: eGFR ≥ 15 ml/min/1.73m^2 Hemoglobin ≥ 9 g/dL Platelets count ≥100,000 mm^3 aPTT ≤ 1.4 x ULN INR < 1.5 AST or ALT ≤ 3 x ULN Negative urine pregnancy test for WOCBP
Pregnancy Test (WOCBP Only)	X	Pregnancy test to be done locally at screening. All WOCBP must have a negative pregnancy test every 30 days (see Protocol Section 6.1 and Appendix 4).
Electrocardiogram (ECG)	X	12-lead ECG should be recorded after the participant has been supine or recumbent for at least 5 minutes and before blood collection (see Section 9.2.15).
Serious Adverse Event (SAE)	X	All SAEs should be collected from the date of written consent through the follow-up period (see Table 2-2, Section 9.2.2, and Appendix 3). Labs performed locally for assessment of SAEs should have reports faxed or scanned and emailed to [redacted].

Table 2-2: Post-Screening Procedural Outline (CV010031)

Procedure	Day 1 Onsite Visit	Day 21 Onsite Visit[a] (±2 days)	Day 60 Onsite/Phone Visit[a,b] (±7 days)	Day 90 Onsite Visit[a,c] (±6 days) (End-of-Treatment)	Day 97 Phone Visit[d] (±2 days) (End-of-Study)	Notes
Study-specific MRI	Xe			X		The baseline MRI should be acquired within 48 hours of the index event and prior to randomization on Day 1. If the baseline MRI cannot be performed within 48 hours of the index event and before randomization, it can be acquired after randomization but must be performed within 72 hours of the index event and up to 24 hours after randomization. In order to randomize a participant prior to the baseline MRI, other neuroimaging (CT or MRI) must be performed to assess eligibility. The protocol-required MRI sequences will be defined in the imaging manual. A second MRI will be performed on Day 90 ± 6 days (based on randomization on Day 1) to accommodate scheduling and scanner availability. Sites are encouraged to schedule the Day 90 MRI at the time of the baseline visit. All participants should remain on study treatment until the Day 90 MRI is performed up to Day 96. In the event that participants are unable or not permitted to attend the Day 90 visit at the study site due to the COVID-19 pandemic, the Day 90 MRI may be performed at an external facility provided that the MRI protocol and scanner have been pre-approved by the central imaging vendor. In the event

Table 2-2: Post-Screening Procedural Outline (CV010031)

Procedure	Day 1 Onsite Visit	Day 21 Onsite Visit[a] (±2 days)	Day 60 Onsite/Phone Visit[a,b] (±7 days)	Day 90 Onsite Visit[a,c] (±6 days) (End-of-Treatment)	Day 97 Phone Visit[d] (±2 days) (End-of-Study)	Notes
						the Day 90 MRI cannot be performed within the + 6-day window, the Day 90 MRI can be performed after the + 6-day window using the study site or an external facility MRI scanner. For these participants, it is understood that they may not be taking study medication past Day 96 (see Section 9.2.12).
Central Safety Laboratory Tests	X[f]	X	X	X		Safety labs: Serum chemistry and hematology (see Section 9.2.16).
Clopidogrel Loading Dose and Aspirin	X					A clopidogrel loading dose is required for study participation. More specifically: Clopidogrel loading dose of 300 mg and 100 mg aspirin will be administered after randomization on Day 1. Clopidogrel loading dose of 300 mg and 100 mg aspirin may be assigned for immediate treatment along with daily 75 mg clopidogrel and 100 mg aspirin upon consenting participant and registering participant in IRT, if considered clinically appropriate Participants who have received a single loading dose of open-label clopidogrel between 300 mg to 600 mg as standard of care prior to obtaining informed consent can also be enrolled in the study. No additional loading dose of clopidogrel is required for such participants after randomization. Following a

Table 2-2: Post-Screening Procedural Outline (CV010031)

Procedure	Day 1 Onsite Visit	Day 21 Onsite Visit[a] (±2 days)	Day 60 Onsite/Phone Visit[a,b] (±7 days)	Day 90 Onsite Visit[a,c] (±6 days) (End-of-Treatment)	Day 97 Phone Visit[d] (±2 days) (End-of-Study)	Notes
						standard-of-care clopidogrel loading dose, the standard-of-care clopidogrel daily dose of 75 mg may be taken prior to randomization. Participants who report taking chronic clopidogrel also require a 300 mg clopidogrel loading dose **unless** the investigator can verify that the participant has taken the daily dose for at least the preceding 3 days. Participants who have received at least 75 mg aspirin as standard of care before randomization and this dose was taken on the same day as randomization, then no additional aspirin is required on Day 1. In this case, 100 mg daily aspirin should be started in the morning of Day 2.
Randomize Participant	X					Participant MUST be randomized within 48 hours of the onset of the index event.
Full Physical Examination				X		See Section 9.2.13.
Brief Physical Assessment		X				Includes organ systems pertinent to the participant's signs, symptoms, or adverse events, e.g., assessment of signs of thromboembolism and bleeding.
Physical Measurements				X		Weight only.

Table 2-2: Post-Screening Procedural Outline (CV010031)

Procedure	Day 1 Onsite Visit	Day 21 Onsite Visit[a] (±2 days)	Day 60 Onsite/Phone Visit[a,b] (±7 days)	Day 90 Onsite Visit[a,c] (±6 days) (End-of-Treatment)	Day 97 Phone Visit[d] (±2 days) (End-of-Study)	Notes
Vital Signs		X		X		Seated blood pressure and heart rate measured after the participant has been resting quietly for at least 5 minutes, and before blood collection (see Section 9.2.14).
Concomitant Medication Use		X	X	X		See Section 7.1.
National Institutes of Health Stroke Scale (NIHSS)[g]	X[e]	X		X		To assess neurological impairment (see Section 9.4.1 and Appendix 5); must be ≤7 at time of randomization.
Modified Rankin Scale (mRS)[g]		X		X		To assess degree of disability or dependence in daily activities (see Section 9.4.3 and Appendix 7).
Montreal Cognitive Assessment (MoCA)[g]	X[h]	X		X		To assess cognitive dysfunction, the MoCA instrument will be completed by the clinical site and sent to a third-party central laboratory for evaluation (see Section 9.4.4 and Appendix 8).
Digit Symbol Substitution Test (subtest of WAIS-IV)[g]	X[h]	X		X		To assess cognitive dysfunction, the DSST (subset of WAIS-IV) instrument will be completed by the clinical site and sent to a third-party central laboratory for evaluation (see Section 9.4.4 and Appendix 9).
Pregnancy Test (WOCBP Only)			X	X		All WOCBP must have a negative pregnancy test every 30 days (see Section 6.1 and Appendix 4).

Table 2-2: Post-Screening Procedural Outline (CV010031)

Procedure	Day 1 Onsite Visit	Day 21 Onsite Visit[a] (±2 days)	Day 60 Onsite/Phone Visit[a,b] (±7 days)	Day 90 Onsite Visit[a,c] (±6 days) (End-of-Treatment)	Day 97 Phone Visit[d] (±2 days) (End-of-Study)	Notes
ECG		X		X		12-lead ECG should be recorded after the participant has been supine or recumbent for at least 5 minutes and before blood collection (see Section 9.2.15).
Adverse Event (AE) Reporting	X	X	X	X	X	NSAE collection begins after randomization through the follow-up period (see Section 9.2.2 and Appendix 3).
Serious Adverse Event (SAE) Reporting	X	X	X	X	X	SAEs collection after written consent through the follow-up period. SAEs must be followed up until resolution or stabilization (see Sections 9.2.2, 9.2.3, and 9.2.5 and Appendix 3). Labs performed locally for assessment of SAEs should have reports faxed or scanned and emailed to [redacted].
Pharmacokinetic (PK) Assessment for BMS-986177[i]	X	X		X		See Section 9.3.1.
Pharmacokinetic (PK) Assessment for Clopidogrel and Aspirin[i]		X		X[j]		See Section 9.3.1.
Pharmacodynamic (PD) Biomarker Sampling (PT, aPTT, and FXI Clotting Activity)[i]	X[f]	X		X		See Section 9.3.2.

Table 2-2: Post-Screening Procedural Outline (CV010031)

Procedure	Day 1 Onsite Visit	Day 21 Onsite Visit[a] (±2 days)	Day 60 Onsite/Phone Visit[a,b] (±7 days)	Day 90 Onsite Visit[a,c] (±6 days) (End-of-Treatment)	Day 97 Phone Visit[d] (±2 days) (End-of-Study)	Notes
Blood for F1.2 and D-dimer	X[f]	X		X		See Section 9.3.2.
Plasma and Serum Exploratory Biomarker Assessments	X[f]	X		X		See Section 9.3.2.
FXI Antigen	X[f]					See Section 9.3.2.
Whole Blood for DNA	X					Day 1 pre-dose. If sample is not collected on Day 1, it can be collected at any time during the study; only one sample is required per participant (see Section 9.3.2). ***Note:*** Collected only in participants in countries and sites where genetic testing is allowed and who opt in to genetic testing as captured on an ICF.
Study Medication Compliance		X	X	X		BMS-986177, placebo, clopidogrel and aspirin (see Section 7.6).
Dispense Study Medication	X	X[k]				The first dose of study medication (BMS-986177 or placebo) should be taken as soon as possible after the baseline MRI assessment, preferably within 2 hours, but no longer than 6 hours. If outside of the 6-hour post-MRI window, the investigator should call the Medical Monitor for guidance. If the baseline MRI is completed after 48 hours from the onset of the index

Table 2-2: Post-Screening Procedural Outline (CV010031)

Procedure	Day 1 Onsite Visit	Day 21 Onsite Visit[a] (±2 days)	Day 60 Onsite/Phone Visit[a,b] (±7 days)	Day 90 Onsite Visit[a,c] (±6 days) (End-of-Treatment)	Day 97 Phone Visit[d] (±2 days) (End-of-Study)	Notes
						event,the first dose of study medication should still be taken immediately after randomization within 48 hours from the onset of the index event.
Study Medication Collection				X		Participant should return all study medication/supplies.

a In the event participants are unable or not permitted to attend an onsite visit due to the COVID-19 pandemic, alternative measures can be considered to obtain required visit assessments as local regulatory requirements permit.

b Day 60 site visit for central clinical safety laboratory testing can occur separate from the phone visit within the ±7-day visit window. If all Day 60 required assessments can be completed onsite, then a phone visit is not required. If the DMC makes a recommendation to discontinue Day 60 lab assessments at the milestone defined in Section 5.1.1, the Day 60 visit will only be a telephone contact. The Sponsor will notify investigators on the decision of the DMC.

c If study treatment is discontinued early, the participant is expected to complete the end-of-treatment assessments, except MRI, at time of study drug discontinuation. For these participants, the Day 90 MRI (± 6 days) as well as Day 97 (± 2 days) visit must be completed at the planned visit days. Other Day 90 visit assessments do not need to be performed if they already were completed at an end-of-treatment visit.

d 7 days after Day 90 MRI. If for any reason a Day 90 MRI is not obtained, then a telephone contact is to be performed at Day 97 ± 2.

e To be conducted prior to randomization. Refer to notes regarding study-specific MRI for instances where the baseline MRI is performed outside of the 48-hour window and the Day 90 MRI is performed outside of the 6-day window.

f To be conducted prior to first dose of study medication.

g In addition to the times specified in this table, assessments are to be obtained at the time of a new stroke (see Appendix 5, 7, 8, and 9).

h May be collected within 48 hours of Day 1.

i Sample should be obtained within 48 hours of new stroke or major bleeding event.

j Sample to be collected for aspirin only.

k Unused Day 1 blister card of study medication and open-label aspirin must be re-dispensed at Day 21.

3 INTRODUCTION

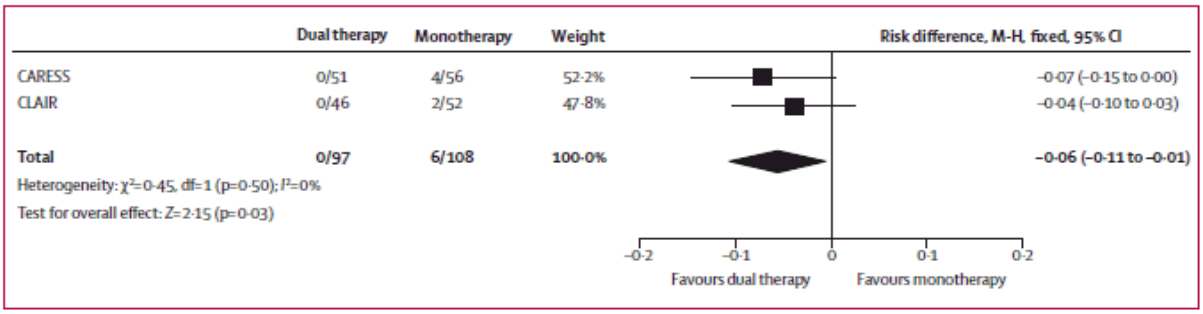
Stroke is a leading cause of death and disability worldwide. Ischemic brain infarction is the most common type of stroke (~80%). Primary brain hemorrhage is a less common cause of stroke (~20%) but is associated with considerable morbidity and mortality. Stroke incidence is strongly linked to age and stroke prevalence is increasing due to the ageing global population. Thromboembolism is common to almost all types of ischemic strokes so that inhibition of thrombosis is a pivotal intervention for stroke prevention. About 1.5 million people have ischemic strokes annually in North America and Europe and about 18 million people worldwide.[1]

The risk of recurrent cerebrovascular events is high in patients who have had a stroke or transient ischemic attack (TIA). The risk of recurrent stroke is particularly high during the initial 90 days following ischemic stroke or TIA. Pooled analyses of observational studies completed in 2007, suggested the early risk of stroke was 9.9%, 13.4%, and 17.3% at 2, 30, and 90 days, respectively.[2,3] Development of specialized acute stroke centers and preventive services have decreased the recurrence rate but it remains unacceptably high. In two recent clinical trials that investigated patients with acute ischemic stroke, the risk of recurrent stroke was 7 to 12% despite treatment with aspirin and other secondary prevention interventions.[4,5] In patients with acute TIA, the rate of subsequent ischemic stroke is somewhat lower, but still high, 4% to 9% at 90 days.[2,3,5] The clinical, time-based definition of TIA has been updated to now include imaging to exclude evidence of tissue damage, but the traditional time-based definition is still commonly used in practice.[6] Clinically defined TIA and stroke form part of a risk continuum and risks of early recurrent stroke, MI and vascular death are similar.[7,8,9]

Accumulating evidence suggests that for patients with strokes associated with large vessel atherosclerosis (CARESS[10], CLAIR[11]) and for patients in whom treatment can be initiated within 12-24 hours after an acute minor stroke or TIA (CHANCE[12], POINT[13]), treatment with aspirin and clopidogrel is more effective than aspirin alone in reducing asymptomatic microembolic signals and the risk of recurrent stroke.

A meta-analysis of data from the CARESS and CLAIR trials below (Figure 3-1) shows that the combination of aspirin and clopidogrel is more effective than monotherapy in reducing the risk of ischemic stroke associated with large vessel atherosclerosis.

Figure 3-1: Meta-analysis Number of Patients with Recurrent Stroke in CARESS and CLAIR for Dual Antiplatelet Therapy *vs* Monotherapy



As shown in Table 3-1, the risk of recurrent ischemic stroke at 90 days with aspirin and clopidogrel was considerable in both CHANCE and POINT and the rate of bleeding was higher with combination therapy than with aspirin alone.

Table 3-1: Rates of Ischemic Stroke and Bleeding in POINT and CHANCE Studies

Study Event	Aspirin (%)	Aspirin + Clopidogrel (%)
CHANCE[12]		
Ischemic Stroke	11.4	7.9
Severe Bleeding	0.2	0.2
Any Bleeding	1.6	2.3
POINT[13]		
Ischemic Stroke	6.3	4.6
Symptomatic ICH	0.1	0.1
Major Hemorrhage not ICH	0.3	0.7
Minor Bleeding	0.5	1.6

Despite the improved efficacy of aspirin and clopidogrel compared to aspirin alone, the residual high risk of recurrent stroke and the higher risk for bleeding with combination therapy highlight the need for a safe and more effective treatment option.

3.1 Study Rationale

A pooled analysis of individual patient data from all randomized trials of aspirin vs. control for secondary prevention after TIA or ischemic stroke as a function of time after the index event, confirmed that medical treatment reduces the risk and severity of early recurrent stroke and that aspirin was the key intervention. Intensification of antiplatelet therapy by adding a P2Y12 inhibitor to aspirin treatment resulted in increased efficacy, but at the cost of more bleeding complications.

Factor Xa inhibitors have recognized therapeutic impact on thrombotic diseases through dose-dependent inhibition of the tissue factor-activated coagulation process. Increasing doses of FXa inhibitors cause progressively more inhibition of hemostasis and efficacy, until bleeding risks limit further increases in FXa doses. Adding a FXa inhibitor to maximized antiplatelet treatment improves efficacy outcomes (as seen below with the COMPASS results) but, again, at the cost of additional bleeding which is a major concern among clinicians when considering antithrombotic therapy in patients with stroke and threatened stroke.

3.1.1 Novel Antithrombotic Mechanism of BMS-986177

BMS-986177 (also known as JNJ-70033093) is a small molecule that binds and inhibits the activated form of human coagulation Factor XI (Factor XIa) with high affinity and selectivity. The

scientific evidence accumulated to date suggest that inhibition of FXIa may provide a novel mechanism for inhibiting intravascular thrombus formation with limited impact on hemostasis.[14]

The rationale for this study is that Factor XIa inhibition has the potential to reduce thrombin generation enough to prevent vascular occlusion and embolism without impairing hemostasis. Whereas Factor Xa inhibitors block the tissue factor-activated coagulation process required for hemostasis, Factor XIa inhibition blocks thrombus formation through the "contact" system, which is not required for normal hemostasis but appears to contribute to pathological thrombus formation. The following observations support this concept: (1) the highest levels of Factor XI activity are associated with a heightened risk of ischemic stroke[15,16,17]; (2) lower levels of Factor XI activity are associated with a reduced risk of ischemic stroke[18,19,20]; (3) Factor XI deficiency is rarely associated with unprovoked major bleeding[21]; (4) although not done in patients with stroke, a Phase 2 study for VTE prophylaxis in patients post total knee replacement provides a proof of concept. The study showed that reducing FXI levels to 20% or less than normal with an antisense inhibitor of FXI synthesis reduced the risk of postoperative VTE compared to enoxaparin, without an increase in bleeding compared to enoxaparin.[14] In patients with ESRD on hemodialysis, single doses of 100 mg and 300 mg BMS-986177 reduced clot formation in the hemodialysis circuits, and was not associated with serious bleeding.[22]

The high residual risk for recurrent stroke seen in the POINT and CHANCE studies (see Table 3-1), even when patients are treated with combination of aspirin and clopidogrel, emphasizes the continuing need for a more effective therapeutic option. Two possible strategies for achieving better efficacy are: (1) more potent antiplatelet therapy. (2) dual pathway inhibition of thrombosis.

3.1.2 More Potent Antiplatelet Therapy

The SOCRATES trial[23] tested the hypothesis that treatment with more potent antiplatelet therapy with ticagrelor would be more effective than treatment with aspirin in patients with TIA or acute minor ischemic stroke. The trial compared ticagrelor (a direct-acting P2Y12 receptor inhibitor antiplatelet agent) *vs.* aspirin 100 mg/day. The 11% reduction in the primary outcome (stroke, myocardial infarction, cardiovascular death) with ticagrelor compared to aspirin was not statistically significant ($p = 0.07$).

A pre-specified exploratory subgroup analysis of the data from the SOCRATES trial[23] showed a significant treatment-by-subgroup interaction suggesting that the risk for the composite endpoint of stroke, myocardial infarction, or death was lower with ticagrelor than aspirin in patients with symptomatic ipsilateral stenosis than in those without ipsilateral stenosis in whom the risk for the composite endpoint was similar with ticagrelor and aspirin. The investigators suggested that this analysis provides empirical evidence of the importance of an understanding of the stroke mechanism and cause in the selecting therapy for early stroke prevention

3.1.3 Dual Mechanisms of Thrombosis Inhibition

Support for this strategy was provided by the recently published results of the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS[24]) trial in which 27,395

patients with stable coronary artery atherosclerosis or peripheral artery atherosclerosis (but without recent stroke) were randomly assigned to receive rivaroxaban 5 mg twice daily (BID), rivaroxaban 2.5 mg BID plus aspirin, or aspirin alone. An analysis for the tertiary outcome of ischemic stroke or uncertain type of stroke showed a relative risk reduction of 49% (absolute risk reduction = 0.7%) with low-dose rivaroxaban plus aspirin *vs.* aspirin alone (nominal p <0.001). Major bleeding increased by 70% (absolute risk increase = 1.2%) with rivaroxaban 2.5 mg BID plus aspirin compared to aspirin alone.[24]

A recent analysis of the patients in COMPASS who had a prior stroke (3.8%=1,041) showed that the annual rate of ischemic stroke was reduced from 3.4% with aspirin alone compared to 0.7% with rivaroxaban plus aspirin [HR = 0.42 (0.19-0.92), nominal p = 0.03)].[25] In addition to a reduction in MACE, a substantial reduction in recurrent ischemic stroke in COMPASS was also observed indicating that the combination of antiplatelet therapy with an anticoagulant has the potential to be more effective than antiplatelet therapy or anticoagulation alone for secondary stroke prevention.

Although the combination of a low dose of rivaroxaban combined with aspirin showed superior efficacy, the risk of bleeding increased more than the risk reduction for ischemic stroke. This result is attributable to the mechanism by which rivaroxaban and other Factor Xa inhibitors reduce thrombosis: dose-dependent inhibition of the tissue factor-activated coagulation process which is required for hemostasis. Increasing doses of FXa inhibitors cause progressively more inhibition of hemostasis which can predispose to bleeding. In contrast to FXa inhibition which impairs hemostasis, FXIa inhibition blocks thrombus formation without impairing hemostasis. The rarity of serious bleeding in people with severe FXI deficiency is consistent with the lack of a significant effect of severely reduced FXI activity on hemostasis.[20]

Accordingly, the combination of BMS-986177 with antiplatelet therapy has the potential to provide superior efficacy for reducing thromboembolic events without predisposing to serious bleeding.

3.1.4 Selection of Treatments

Identification of the putative mechanism of stroke is critical for selecting the treatment that is most likely to be effective. The totality of evidence from clinical trials to date support the use of more intensive antiplatelet therapy than treatment with aspirin alone to reduce the risk of stroke associated with atherosclerosis in the major cerebral arteries and aortic arch.

Accordingly, in this study, in a population with acute ischemic stroke associated with large vessel atherosclerosis, the combination of aspirin and clopidogrel will be used as a background therapy. The combination of a wide range of doses of BMS-986177 with aspirin and clopidogrel is expected to provide a robust dose-response relationship and to identify one or more doses that will provide improved efficacy without an increased risk of bleeding that exceeds absolute risk reduction for the composite endpoint of new ischemic stroke and new covert brain infarction.

3.2 Background

3.2.1 Phase 1 and 2a Studies with BMS-986177

BMS-986177 is currently being investigated in a number of studies in humans including: (1) single ascending and multiple ascending dose study; (2) drug-drug interactions with itraconazole, diltiazem, rifampin, aspirin, and aspirin plus clopidogrel; (3) clinical pharmacology studies of special populations including participants with end-stage renal disease (ESRD) undergoing hemodialysis, participants with renal impairment, and participants with hepatic impairment; (4) relative bioavailability and (5) Japanese PK study. To date, no dose-limiting safety findings have been observed in these studies.

The first-in-human (FIH) study with BMS-986177 investigated single oral doses between 4 - 500 mg and multiple oral doses between 5 - 500 mg over a 14-day period. In the single-dose portion of the study, dose-proportionality was observed between 20 - 200 mg QD with no greater increase in exposure observed at 300 mg, believed to be due to solubility-limited absorption. Co-administration of a high-fat diet at 200 mg and 500 mg was associated with ~1.2-fold and ~2-fold increases in exposure, respectively. Table 3.2.1-1 summarizes the clinical pharmacology of BMS-986177.

Table 3.2.1-1: Highlights of Clinical Pharmacology after Oral Administration of Single and Multiple Doses of BMS-986177 to Healthy Participants and Participants with Renal or Hepatic Impairment

PK Properties	BMS-986177 Clinical PK Results
T_{max}	2 to 4 hours in a fasted state with rapid absorption and quick onset of PD effect
Half-life ($T_{1/2}$)	~11 hours (terminal $T_{1/2}$); supports BID or QD dosing
Accumulation Index (AI)	Minimal accumulation: AI = 1.13 to 1.40 for AUC (dose range 20 to 200 mg in MAD study; for QD dosing only)
Exposure	• Average C_{max}: 15.4 to 7595 ng/mL; • Average AUC:172 to 95110 ng•hr/mL
Dose Proportionality	• Single oral doses: greater than dose proportional from 4 to 20 mg; dose proportional between 20 and 200 mg • Multiple oral doses: greater than dose proportional from 5 to 20 mg; dose proportional between 20 and 200 mg
Renal Impairment (normal renal function vs. moderate or severe renal dysfunction)	• Renal Clearance: ~10% • Similar C_{max} between all renal function groups • When compared to normal renal function (@ eGFR of 90 mL/min/1.73 m^2): - moderate impairment (@ eGFR of 30 mL/min/1.73 m^2): 39%↑ in $AUC_{(0-T)}$; 41%↑ in $AUC_{(0-INF)}$ - severe impairment (@ eGFR of 15 mL/min/1.73 m^2 not on dialysis): 50%↑ in $AUC_{(0-T)}$; 54%↑ in $AUC_{(0-INF)}$

Table 3.2.1-1: Highlights of Clinical Pharmacology after Oral Administration of Single and Multiple Doses of BMS-986177 to Healthy Participants and Participants with Renal or Hepatic Impairment

PK Properties	BMS-986177 Clinical PK Results
Hepatic Impairment (normal hepatic function vs mild or moderate hepatic impairment)	• Primarily metabolized in the liver – Similar C_{max} and $AUC_{(0\text{-}INF)}$ between normal, mild and moderate hepatic impairment groups • Compared to normal participants – Mild hepatic impairment (Child Pugh A category): 18% ↑ in C_{max} and $AUC_{(0\text{-}INF)}$ – Moderate hepatic impairment (Child Pugh category B): 14% ↑ in C_{max} and no change in $AUC_{(0\text{-}INF)}$ • When accounting for changes in protein binding, the differences in normal participants compared to: – Mild hepatic impairment (Child Pugh A category): 30% ↑ in C_{max} and 29% ↑ in $AUC_{(0\text{-}INF)}$ – Moderate hepatic impairment (Child Pugh category B): 41% ↑ in C_{max} and 24% ↑ in $AUC_{(0\text{-}INF)}$
Food Effect	Small food effect at 200 mg (53% ↑ in C_{max}; 39% ↑ for AUC)
Metabolites	No major or active metabolites
CYP3A4 Inhibitors or Inducer DDI	• Itraconazole: 150% ↑ in AUC; 28% ↑ in C_{max} • Diltiazem: 38% ↑ in AUC; 9% ↑ in C_{max} • Rifampin: 85% ↓ in AUC; 78% ↓ in C_{max}

A multicenter, cross-over, randomized, Phase 2a proof-of-concept study in participants undergoing hemodialysis for ESRD showed that single doses up to 300 mg of BMS-986177 were safe and well tolerated; no serious bleeding or other serious adverse events occurred. Exploratory efficacy assessment showed that the extent of clot formation in the hemodialysis circuit was similar with BMS-986177 and the active comparators (unfractionated heparin and enoxaparin). This result suggests that BMS-986177 has clinically meaningful antithrombotic activity at the doses tested. Detailed information on BMS-986177 Phase 1 and Phase 2a studies is provided in the Investigator's Brochure.[26]

BMS-986177 combined with antiplatelet therapy has the potential to be safe and more effective than antiplatelet therapy alone. A drug-drug interaction study (CV010027[27]) showed that BMS-986177 200 mg BID taken with aspirin was safe and well tolerated over a 7-day period in healthy participants, and bleeding time did not increase significantly. In another drug-drug interaction study in healthy participants, BMS-986177 200 mg was given twice daily (BID) for 5 days, with and without clopidogrel and aspirin. Clopidogrel was given as 300 mg on Day 1 followed by 4 days of 75 mg clopidogrel, and 325 mg aspirin was administered once daily [QD] for 5 days. There were no serious bleeding events reported from any of the 113 healthy participants treated in this study[28]. A few minor bleeding events (e.g., contusion, venipuncture site bruise, gingival bleeding, and anal fissure bleeding) occurred in either subjects who received dual antiplatelet treatment plus BMS-986177, or in participants who received dual antiplatelet treatment

without BMS-986177, or in participants who received mono antiplatelet treatment (either clopidogrel or aspirin) alone, indicating no trend towards any treatment arms. These findings are consistent with the notion that FXIa inhibition is associated with a low risk of bleeding, and support the proposed clinical trial with BMS-986177, aspirin and clopidogrel.

3.3 Benefit/Risk Assessment

Anticoagulation has the potential to cause major bleeding which has been demonstrated in all clinical trials (SPIRIT[29], WARSS[30], WASID[31], ESPRIT[32], ARISTOTLE[33], RELY[34], ROCKET AF[35], COMPASS). And the risk of bleeding associated with anticoagulation is heightened by concomitant use of aspirin and other antiplatelet drugs (ARISTOTLE[33], APPRAISE-2[36], ATLAS-2[37], COMPASS[24]). Concern about bleeding is a major obstacle to use of anticoagulation, even when clinical trial data show that the absolute risk of bleeding is lower than the risk of thromboembolic events.[38]

A number of scores based on clinical factors (HEMORRHAGES[39], ATRIA[40], and HAS-BLED[41]) have been developed to predict the risk of major bleeding. However, none of the currently available scores are sufficiently accurate in predicting major bleeding in patients with non-valvular atrial fibrillation (NVAF) to be used as a rationale to withhold anticoagulation to reduce the risk of thromboembolic events, especially stroke.[42] In addition, some clinical factors (hypertension, stroke, renal impairment) included in bleeding scores also increase the risk of thromboembolic events.

DOACs are a major advance in improving the safety of anticoagulation. The risk of intracranial hemorrhage, the most devastating kind of bleeding, is at least 50% lower with DOACs compared to warfarin in patients with NVAF.[43]

A recent publication describes uniform definitions of cardiovascular and stroke outcomes developed by the Standardized Data Collection for Cardiovascular Trials and Initiatives (SCTI) and the U.S. Food and Drug Administration (FDA).[44] According to Hicks et al, “The aim is for clinical trials to apply the stroke definition to assess the clinically relevant consequences of vascular brain injury”.

In the context of the SCTI definition, a clinically meaningful benefit of treatment is not only to decrease the number of strokes but also to mitigate the clinical consequences of ischemic brain infarction. Since no single outcome measure can describe all the dimensions of brain infarction[45], we plan to use multiple instruments to assess the clinical consequences of brain infarction: National Institute of Health Stroke Scale/Score (NIHSS), modified Rankin Scale (mRS), Montreal Cognitive Assessment (MoCA), and Digit Symbol Substitution Test (DSST; subtest of WAIS-IV).

The available preclinical and clinical evidence suggest that direct inhibition of Factor XIa by BMS-986177 has the potential to reduce the risk of thromboembolic events with a lower risk of major bleeding than currently available DOACs, even in combination with aspirin + clopidogrel, thus providing a favorable benefit/risk.

While bleeding was not observed to any significant degree at high doses of BMS-986177 either in healthy participants or in patients with ESRD undergoing hemodialysis, there is a potential risk of bleeding with any antithrombotic agent. Therefore, participants will be closely monitored for bleeding with oversight of the study by an independent Data Monitoring Committee (DMC).

More detailed information about the known and expected benefits and risks, as well as reasonably anticipated adverse events (AEs) of BMS-986177, is provided in the Investigator's Brochure.[26]

4 OBJECTIVES AND ENDPOINTS

Objectives and endpoints for CV010031 can be found in Table 4-1. Definition and details related to study endpoints can be found in the Study Events Assessment Manual.

Table 4-1: Objectives and Endpoints for CV010031

Objective	Endpoints
Primary	
To estimate the dose-response relationship of BMS-986177 in participants with ischemic stroke or TIA treated with aspirin and clopidogrel	Composite of new ischemic stroke during the treatment period and new covert brain infarction (FLAIR + DWI) detected by MRI at Day 90 (MRI assessed by central review)
Secondary	
To assess the rate of major bleeding after treatment with BMS-986177 relative to placebo	Event rate based on bleeding according to Bleeding Academic Research Consortium (BARC) Type 3 and 5
To assess the rate of all bleeding after treatment with BMS-986177 relative to placebo	Event rate based on BARC, ISTH and PLATO-defined criteria
To compare the rate of the composite of new ischemic stroke and new covert brain infarction detected by MRI at 90 days on treatment with BMS-986177 compared to placebo	Rate of the composite of new ischemic stroke during the treatment period and new covert brain infarction (FLAIR + DWI) detected by MRI at 90 days
To assess the effect of BMS-986177 on characteristics of brain lesions on Day 90 MRI	Location, number, and volume of new FLAIR + DWI lesions
To compare the rate of the composite of new ischemic stroke, myocardial infarction (MI) and all-cause mortality during treatment with BMS-986177 *vs.* placebo	Event rates for new ischemic non-fatal stroke, non-fatal MI, and all-cause death during the treatment period
To assess stroke severity, neurological, and cognitive function following BMS-986177 treatment *vs.* placebo	National Institutes of Health Stroke Scale (NIHSS), Modified Rankin Scale (mRS), Montreal Cognitive Assessment (MoCA), and Digit Symbol Substitution Test (subtest of WAIS-IV) at baseline, on Days 21 and 90, and at the time of a new stroke event.
To assess the safety and tolerability of BMS-986177	Adverse events, vital signs, physical exams, electrocardiogram (ECG), and clinical laboratory results
To assess the pharmacokinetics (PK) of BMS-986177 and potential effects of covariates on exposure	Estimated clearance (CL) and volume of distribution (Vd) and effect of body weight, age, gender, race, renal function, liver function, concomitant medications

Table 4-1: Objectives and Endpoints for CV010031

Objective	Endpoints
To assess the dose-response of BMS-986177 on pharmacodynamic (PD) biomarkers	% change from baseline in aPTT and Factor XI clotting activity during treatment
Exploratory	
To assess the effect of BMS-986177 on characteristics of cerebral microbleeds (CMBs), hemorrhagic transformation of ischemic stroke and asymptomatic intracranial bleeding on Day 90 MRI	Incidence and characteristics of CMBs, hemorrhagic transformation of ischemic stroke and asymptomatic intracranial bleeding on Day 90 MRI
To explore the exposure-response (E-R) relationship of BMS-986177 on efficacy endpoints	New ischemic non-fatal stroke, non-fatal MI, and all-cause death during the treatment period
To explore the E-R relationship of BMS-986177 on major bleeding	Bleeding according to BARC Type 3 and 5 definitions
To assess the PK of clopidogrel (and metabolites), aspirin and salicylic acid	Clopidogrel (and metabolites), aspirin and salicylic acid plasma concentrations
To explore the E-R relationship of BMS-986177 on aPTT and Factor XI clotting activity	% change from baseline in aPTT and Factor XI clotting activity during treatment
To explore biomarkers related to FXI pathway, stroke, thrombosis/hemostasis, inflammation and cardiovascular diseases, and their relationship to BMS-986177 treatment and selected endpoints	These markers may include, but are not limited to: plasma D-dimer, PT, F1.2, and Factor XI antigen.

5 STUDY DESIGN

5.1 Overall Design

The study is a multi-center, Phase 2, randomized, double-blind, placebo-controlled, dose-ranging trial. Eligible participants will be screened for potential inclusion into the study as soon as possible after presentation and randomized within 48 hours of the index event.

Following signing of informed consent, participants will receive aspirin 100 mg and a single loading dose of clopidogrel 300 mg. Participants will then be randomized to receive BMS-986177 or placebo, plus open-label uncoated aspirin 100 mg in combination with clopidogrel 75 mg QD for the next 21 days. Participants will continue treatment from Day 22 through Day 90 with BMS-986177 or placebo, plus open-label 100 mg uncoated aspirin only.

An MRI of the brain will be performed on Day 90 ± 6 days (based on randomization on Day 1). All participants should remain on study treatment until the Day 90 MRI is performed up to Day 96.

The enrollment period for this trial will last approximately 36 months.

Screening Period:

- All study assessments should occur within the first 48 hours after the index event, following participant consent.

- A baseline MRI should be acquired within 48 hours of the index event and prior to randomization on Day 1. If the baseline MRI cannot be performed within 48 hours of the index event and before randomization, it can be acquired after randomization but must be performed within 72 hours of the index event and up to 24 hours after randomization. In instances where the baseline MRI is completed after 48 hours from the onset of the index event, the first dose of study medication should still be taken immediately after randomization within 48 hours from the onset of the index event.
- Within 48 hours of the index event, and prior to randomization, all participants will have a Doppler ultrasound, computed tomography angiogram (CTA), magnetic resonance angiogram (MRA), or catheter angiography to assess for the presence of intracranial or cervical arterial atherosclerotic plaque, ulceration, or thrombus that is proximal to the index lesion. Use of available vascular imaging showing a qualifying lesion prior to the stroke event is allowed for participants who cannot complete the vascular imaging within 48 hours of the index event.
- At screening, the following will be obtained: physical examination, physical measurements, local clinical laboratory tests (including pregnancy test for WOCBP), vital signs, ECG, and medical history.
- The following functional/disease severity assessments are to be completed at screening for eligibility assessment: ABCD2, NIHSS, and mRS.

Double-blind Treatment Period:

- The double-blind treatment period will be from Day 1 to Day 90.
- During the initial phase of the study, a minimum of 800 participants will be randomized to one of the following 4 doses of BMS-986177: 25 mg daily (QD); 25 mg, 50 mg, or 100 mg twice daily (BID); or placebo. Twenty-five percent (25%) of the participants will be randomized to the placebo arm, and the rest of the participants will be randomized equally to the 4 doses of BMS-986177.
- All participants will be treated with open-label uncoated aspirin, 100 mg QD, and clopidogrel, 75 mg QD (after a single 300-mg clopidogrel loading dose + aspirin 100 mg one day prior), for 21 days, followed by aspirin alone from Day 22 to Day 90.
- On Day 1, prior to the initial dose of study medication, the following will be obtained: central clinical laboratory tests for safety, PD samples, exploratory biomarker samples, and optional pharmacogenomic samples.
- Assessments of stroke severity, disability, impact of stroke on daily activities, and cognitive function will be collected at times specified in Table 2-1 and Table 2-2.
- A Day 60 visit is required for central clinical safety laboratory sample within a ±7-day visit window for approximately 450 participants, after which the DMC will determine if such safety laboratory assessment will be continued, reduced, or discontinued. The DMC will review safety data, including clinical laboratory and any available imaging results when approximately 450 participants have completed the Day 21 visit. The DMC will recommend if further monitoring of Day 60 laboratory samples is needed. The DMC recommendation regarding the Day 60 clinical safety laboratory sample will be communicated to investigators by the study Sponsor.
- A telephone contact is required on Day 60 if all the respective assessments have not been completed onsite.

- Onsite visits will be required on Days 21 and 90 (end-of-treatment visit). At these visits, the following will be obtained: central laboratory tests for safety, PK, PD, and exploratory biomarkers.
- In the event participants are unable or not permitted to attend an onsite visit due to the COVID-19 pandemic, alternative measures can be considered to obtain required visit assessments as local regulatory requirements permit.
- The randomization of participants to the 200-mg BID dose may occur in a staggered approach after a minimum of 800 participants have been randomized. The decision to proceed with the 200-mg BID dose group will depend on the evaluation of the population, the DMC review of efficacy and safety data, and an assessment of whether it is safe to randomize participants to that dose group.
- When approximately 800 participants have been randomized, randomization for the placebo group will be used to achieve a 2:1 ratio relative to each treatment arm by the end of the study. Once a decision to add the 200-mg BID dose group has been made, randomization will be revised to achieve a target 2:1:1:1:1:1 (placebo: 25 mg QD: 25 mg BID: 50 mg BID: 100 mg BID: 200 mg BID) by the end of this study.
- All participants will also have an MRI of the brain performed on Day 90 ± 6 (based on randomization on Day 1) to accommodate scheduling and scanner availability. Sites are encouraged to schedule the Day 90 MRI at the time of the baseline visit. All participants should remain on study treatment until the Day 90 MRI is performed up to Day 96. In the event that participants are unable or not permitted to attend the Day 90 onsite visit due to the COVID-19 pandemic, the Day 90 MRI may be performed at an external facility provided that the MRI protocol and scanner have been pre-approved by the central imaging vendor. In the event the Day 90 MRI cannot be performed within the ± 6-day window, the MRI can be acquired outside the + 6-day window using the study site or an external facility MRI scanner. For these participants, it is understood that they may not be taking study medication past Day 96.
- Investigators will determine the management of participants who have a clinical event during the study and assess events, including those lacking an MRI.
- A telephone contact to assess efficacy and safety events will be required for all participants. For participants completing treatment, this contact will be timed within 7 days after the end of the treatment period and after the Day 90 MRI. For participants not completing treatment, an MRI is to be scheduled at Day 90, with a telephone contact scheduled 7 days after the Day 90 MRI; if for any reason a Day 90 MRI is not obtained, then a telephone contact is to be performed at Day 97 ± 2.
- Any participant who discontinues study drug treatment for any reason during the trial will require a Day 90 MRI, followed by the study discharge telephone visit (Day 97 ± 2).
- Participants who permanently discontinue study treatment early should complete the end-of-treatment assessments, except MRI, at time of study drug discontinuation. For these participants, the Day 90 MRI as well as Day 97 visit must be completed at the planned visit days. Other Day 90 visit assessments do not need to be performed if they already were completed at the end-of-treatment visit. In addition, a follow-up telephone contact between discontinuation and Day 90 MRI is encouraged for participants who permanently discontinue study treatment early.

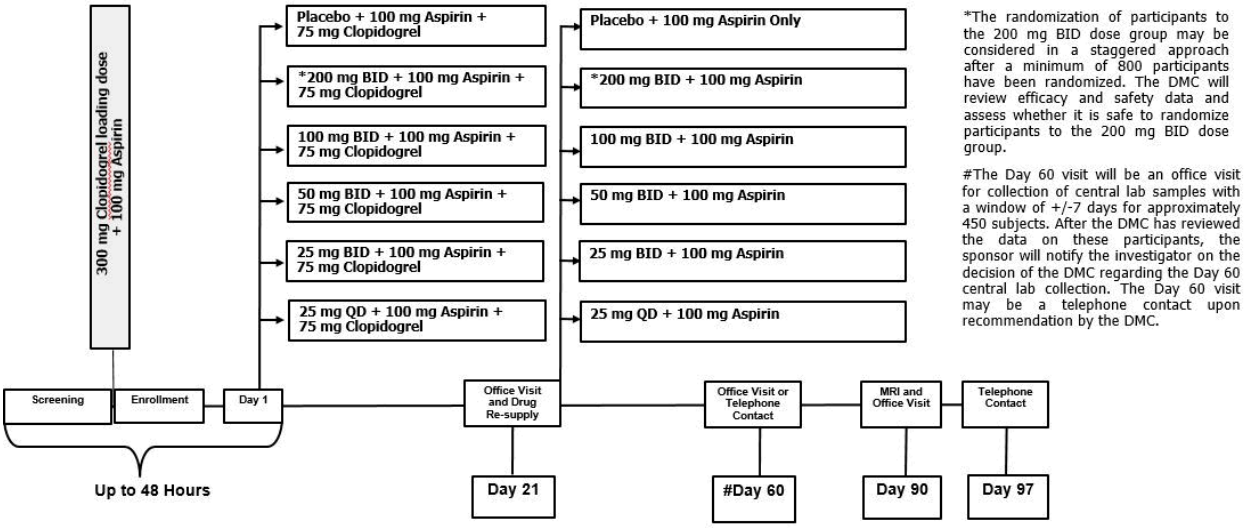
- For participants who withdraw consent for follow-up, there should be documentation of the reason for withdrawal. Study staff should explicitly seek information about the possible contribution of AEs to the participant's desire to withdraw and document any AEs that are identified in the AE section of the CRF.
- Early permanent discontinuation of study medication should be distinguished from withdrawal of consent for follow-up visits, telephone contacts, or medical records checks. Participants requesting withdrawal from the follow-up should be informed that withdrawal of consent for follow-up will result in loss of important information about the benefits and risks of BMS-986177.

Follow-up Period:

- To be discharged from the study, a telephone contact to assess efficacy and safety events will be required for all participants. For participants completing treatment, this contact will be timed within 7 days after the end of the treatment period and after the Day 90 MRI. For participants not completing treatment, an MRI is to be scheduled at Day 90, with a telephone contact scheduled 7 days after the Day 90 MRI. If for any reason a Day 90 MRI is not obtained, then a telephone contact is to be performed at Day 97 ± 2.

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

Figure 5.1-1: Study Design Schematic



Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. Participants will be closely monitored for AEs throughout the study. Blood samples will be collected for PK analysis for up to 24 hours after study drug administration. Approximately 200 mL of blood will be drawn from each participant during the study.

Rationale for Imaging Endpoints

Brain infarction detected by MRI frequently occurs without focal neurological signs or symptoms associated with acute stroke. The difference between clinically diagnosed stroke and "covert/silent" brain infarctions detected by MRI is not pathogenesis, but rather size and location (sparing motor and speech areas of the brain) of the lesion. Covert, MRI-detected brain infarctions can have clinically meaningful neurological consequences. Covert brain infarctions, by definition, do not produce symptoms of TIA or stroke but they can be associated with neurologic dysfunction such as cognitive impairment and gait abnormality.[46,47,48] Furthermore, covert brain infarctions are associated with an up to 5-fold increase in the risk of future stroke, even after adjustment for other risk factors, and with an increased risk of dementia (HR = 6.12, 95% CI: 1.82 to 20.54) independently of vascular risk factors and interim stroke.[48,49,50] Clinicians consider covert brain infarctions clinically relevant, and this is now reflected in the recent American Heart Association Scientific Statement on preventing stroke in patients with apparently "silent" cerebrovascular disease, offering guidance for clinical evaluation and management of these participants.[48]

MRI-detected brain infarction has been included as an endpoint in stroke prevention trials of transfusion in sickle cell anemia[51] and closure of patent foramen ovale[52] and as an exclusive efficacy endpoint for a neuroprotectant during endovascular intracranial aneurysm repair[53].

In summary, MRI-detected brain lesions are an accepted measure of brain ischemia and tissue necrosis that can be used to assess efficacy in a Phase 2 dose-finding study in participants with acute non-hemorrhagic stroke or TIA. The rate of new, covert, MRI-detected brain infarctions (~12% at Day 90) is at least 2- to 3-fold times higher than the cumulative rate of acute stroke (~5% with aspirin and clopidogrel at 90 days in the POINT trial[13]). Therefore, the rate (~15%) of the composite endpoint of covert, MRI-detected brain infarction and stroke should be sufficient to detect a treatment effect across doses in this dose-ranging study with a manageable sample size.

5.1.1 Data Monitoring and Other External Committees

Data Monitoring Committee (DMC)

An independent DMC, whose activities will be described in a charter, will monitor the study and be comprised of experienced clinicians, trialists, and statistical experts. The DMC will review efficacy and safety data at designated times during the trial with the purpose of each review defined in the DMC charter. After approximately 450 participants have completed the Day 21 visit, the DMC will recommend if the Day 60 central laboratory samples are still needed. The DMC recommendation regarding the Day 60 clinical safety laboratory sample will be communicated to the investigator by the study Sponsor.

The DMC will review efficacy and safety data after a minimum of 800 participants have been randomized, and assess whether it is safe to randomize participants to the 200-mg BID dose arm.

The DMC will use their clinical and statistical judgment to evaluate pertinent trial data and may recommend early termination of an individual study arm or the entire trial for important safety

concerns that are felt to outweigh potential benefits. Details of the DMC activities will be described in a DMC charter.

Steering Committee (SC)

The SC will consist of the Lead Investigator, who will serve as SC Chair. Other members will include: national leaders from other countries, other experts, and Sponsor representatives. The SC will be responsible for scientific aspects of the study and will ensure that the study execution and management are of the highest quality. The SC will convene regularly to discuss and report on ongoing supervision of the study.

5.2 Participants

Approximately and up to 2350 participants from approximately 30 countries and approximately 380 clinical research sites will be randomized using a competitive enrollment approach (see Section 10.1).

5.3 End-of-Study Definition

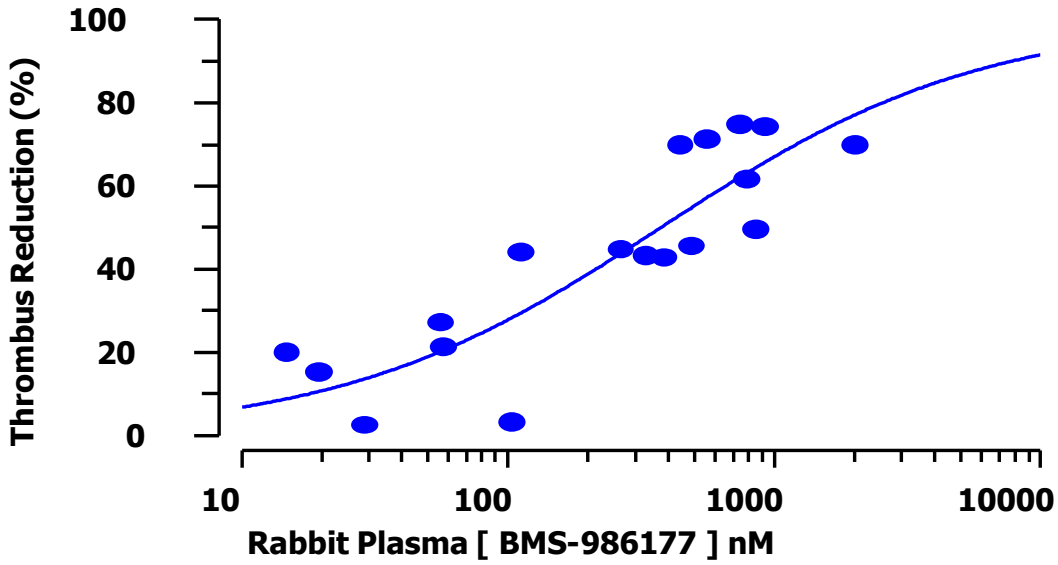
The start of the study is defined as the date the first participant is screened. End-of-study is defined as the date the last participant completes the Day 97 discharge visit. Study completion is defined as the final date on which data for the primary endpoint was, or is expected to be, collected, if this is not the same as the end-of-study definition. The approximate duration of the study for each participant will be 99 days, which includes a maximum 48-hour screening period, a 90-day treatment period and 7-day health follow-up period.

5.4 Justification for Doses

5.4.1 Identification of Effective Doses of BMS-986177

Identification of effective doses of BMS-986177 was based on inhibition of thrombus formation in a rabbit model of electrically-induced thrombus in the carotid artery of rabbits (ECAT). The rabbit ECAT model has been calibrated against clinical results in venous thromboembolism prevention (VTEp) based on apixaban. In this model, targeting the concentration that led to 50% reduction in thrombus weight was correlated with the steady-state trough concentration of the clinical dose of apixaban. In the rabbit ECAT model, BMS-986177 caused a dose-dependent decrease in both clot weight (Figure 5.4.1-1) and preservation of blood flow without a significant increase in bleeding time. The dose of BMS-986177 in humans that is equivalent to the EC_{50} in the rabbit ECAT model is 55 nM. Free fraction and Ki against human *vs* rabbit factor XIa were used to estimate the human equivalent dose.

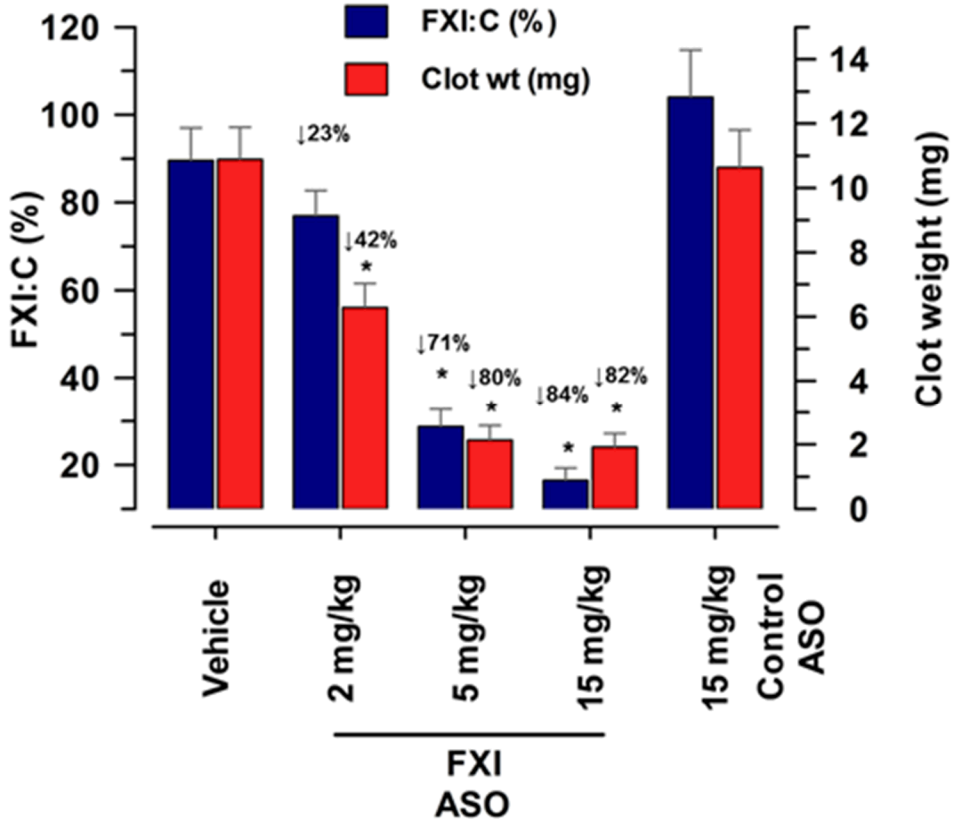
Figure 5.4.1-1: Exposure-dependent Reduction in Thrombus Weight and Human Equivalent Concentration Targets Based on BMS-986177



A Phase 2 study for VTE prophylaxis post total knee replacement provides the only published data on the clinical safety and efficacy of reducing Factor XI activity. Patients were treated for 36 days prior to surgery with an antisense oligonucleotide (ASO) to reduce the level of Factor XI. The study showed a dose-dependent reduction in the risk of VTE events compared to enoxaparin. Doses that did not reduce FXI levels to 20% or less of normal did not reduce the risk of VTE events compared to enoxaparin.[14]

Figure 5.4.1-2 shows the dose-dependent decrease in FXI levels and clot weight observed in the rabbit ECAT model with ASO-induced inhibition of FXI. Based on the dose-dependent reduction of FXI concentrations observed in the ASO VTEp study, a trough concentration of approximately 150 ng/mL of BMS-986177 was necessary to achieve an antithrombotic effect equal to the 80% reduction in FXI level in the rabbit ECAT model.

Figure 5.4.1-2: Reduction in FXI Concentration Based on Factor XI Antisense Oligonucleotide (FXI ASO) Compound Used in Phase 2 VTE Study



Based on data obtained from healthy participants, population pharmacokinetic modeling indicates that doses likely to achieve the trough concentration targets based on apixaban and ASO for a VTEp study are between 50 - 200 mg QD and 25 - 100 mg BID. The data indicating coverage of the target concentrations in the rabbit ECAT model for both apixaban and the FXI inhibitor ASO, supports the potential for BMS-986177 to provide similar or greater efficacy in patients.

Finally, a lower risk of bleeding is anticipated with inhibition of Factor XIa than with inhibition of Factor Xa, based on the mechanistic rationale for targeting the intrinsic pathway via inhibition of Factor XIa and therefore testing high doses of Factor XIa inhibition is warranted for investigation of a maximized dose-response.

5.4.2 BMS-986177 with Aspirin + Clopidogrel

No clinical studies have assessed the effect of a combination of aspirin and Factor XIa inhibition or the combination of Factor XIa inhibition and aspirin and clopidogrel on efficacy or safety outcomes in any patient population. Results from a drug interaction study in healthy participants indicated that BMS-986177 and aspirin can be administered together without safety concerns. Similarly, a drug interaction study of dual antiplatelet therapy (aspirin + clopidogrel) and

BMS-986177 demonstrated that BMS-986177 may be administered with each antiplatelet agent separately and in combination with low risk of serious bleeding.

The results of the COMPASS trial[24] showed that, when combined with aspirin, a dose of rivaroxaban only 25% of that used for stroke prevention in participants with nonvalvular atrial fibrillation (NVAF) reduced the risk of ischemic stroke by 51% compared to aspirin alone. The doses of rivaroxaban used in combination with aspirin in COMPASS was half the dose of rivaroxaban used in VTEp. Assuming a similar synergistic effect as observed with rivaroxaban and aspirin, BMS-986177 combined with aspirin in addition to clopidogrel is expected to provide a favorable risk-to-benefit ratio for secondary stroke prevention. Based on the totality of this information, 50 - 150 mg QD or 25 - 50mg BID of BMS-986177 are the likely ranges of efficacious doses for secondary stroke prevention. However, investigating a wide dose range to establish a robust dose-response curve for BMS-986177 is critical to confirm these predictions.

Accordingly, a dose-response design will be used to investigate a range of doses of BMS-986177 co-administered with aspirin and clopidogrel to identify the most favorable dose and dosing regimen for a secondary stroke prevention population for two reasons: (1) to evaluate the efficacy of BMS-986177 combined with aspirin and clopidogrel and (2) to establish an accurate and precise dose-response relationship for BMS-986177.

Dose strengths selected for capsule development of BMS-986177 in Phase 2 are 25 and 100 mg.

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent
   a) Participants ≥40 years of age (or legally acceptable representatives, as per country guidelines) from whom a signed and dated written consent for participation has been obtained.
2) Type of Participant and Target Disease Characteristics
   a) **Ischemic stroke:** a neurological deficit attributable to a non-lacunar acute brain infarction detected by neuroimaging (CT or MRI) and relevant to the clinical symptoms.

      AND

      National Institutes of Health Stroke Score (NIHSS) ≤7 at time of randomization.

      AND

      Evidence of relevant intracranial or cervical arterial atherosclerotic plaque, ulceration or thrombus in a feeding artery documented by imaging (either Doppler ultrasound or CTA or MRA or catheter angiography).

      Note: Atherosclerotic plaque does not need to be severe or stenotic, but must be visible. Participants with complete occlusion of a cervical carotid or intracranial artery that is proximal to the index lesion should be excluded.

AND

Modified Rankin Score (mRS) ≤3 before the index event (pre-morbid).

b) **TIA**: acute onset neurological deficit attributable to focal ischemia of the brain by history or examination, with complete resolution of the deficit and no brain infarction on neuroimaging (CT or MRI).

AND

ABCD[2] Score ≥6[3] or presence of motor symptoms.

AND

Evidence of relevant intracranial or cervical arterial atherosclerotic plaque, ulceration or thrombus in a feeding artery documented by imaging (either Doppler ultrasound or CTA or MRA or catheter angiography).

***Note**:* Atherosclerotic plaque does not need to be severe or stenotic, but must be visible. Participants with complete occlusion of a cervical carotid or intracranial artery that is proximal to the index lesion should be excluded.

AND

Modified Rankin Score (mRS) ≤3 before the index event (pre-morbid).

3) Two MRI scans are required for participation in this study (see Section 9.2.12). Therefore, participants must have a body habitus suitable for MRI and cannot have any contraindications to the performance of the MRI (see Section 7.7.2.1).
4) No contraindication to clopidogrel or aspirin and suitable for treatment with aspirin 100 mg per day for at least 90 days.
5) Age and Reproductive Status
   a) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study treatment.
   b) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of treatment with BMS-986177 plus 5 half-lives of study treatment plus 30 days (duration of ovulatory cycle) for a total of 34 days post-treatment completion.
   c) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatment BMS-986177, plus 5 half-lives of the study treatment, plus 90 days (duration of sperm turnover) for a total of 94 days post-treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.
   d) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active, or are not of childbearing potential, are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

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

6) Enrollment of subjects who have received thrombolytic therapy or mechanical thrombectomy (without stenting) for the treatment of the index event is permitted if all of the following conditions are met:

- At least 24 hours have elapsed between end of IV thrombolytic use/thrombectomy and first dose of study medication.
- Neuroimaging (either clinical imaging or study MRI) after IV thrombolytic therapy/ post-thrombectomy excludes any hemorrhagic transformation.
- NIHSS ≤ 7 at time of randomization.
- Post-thrombolytic therapy/post-thrombectomy INR ≤ 1.5, aPTT ≤1.4 prior to study treatment administration.
- No contraindications have been identified that in the opinion of the investigator would preclude start of study medication (e.g. large infarct volume, procedure-related bleeding).
- All other study criteria are met.

In addition, we recommend following local practice and considering fibrinogen > 150 mg/dL before initiation of study treatment.

6.2 Exclusion Criteria

1) Medical Conditions
   a) Predicted inability to swallow study medication.
   b) Women who are pregnant or breastfeeding.
   c) Any condition that, in the opinion of the investigator, contraindicates anticoagulant therapy or would have an unacceptable risk of bleeding such as a large infarct volume (per investigator discretion) or uncontrolled hypertension.
   d) Hemorrhage, tumor, arteritis, large vessel dissection, arteriovenous malformation (AVM) or other pathology that could account for index symptoms must be excluded by CT or MRI interpreted locally.
   e) Symptomatic carotid stenosis or intracranial artery stenosis for which endarterectomy or angioplasty is planned within 90 days.
   f) Not applicable per global protocol amendment 06.
   g) Any condition for which chronic anticoagulation is indicated and expected to be initiated (eg, NVAF, DVT, PE).
   h) Requirement for continued use of dual anti-platelet therapy (DAPT) for more than 21 days or non-aspirin antiplatelet therapy or anticoagulant for another medical condition (eg, prophylaxis for venous thromboembolism).

      Note: Treatment with clopidogrel, aspirin, dipyridamole or another P2Y12 inhibitor prior to enrollment is allowed. Treatment with aspirin at a different dose before enrollment is also allowed. All participants must transition to the protocol-defined

treatments and doses at randomization. No clopidogrel loading dose is needed for participants who received a clopidogrel loading dose prior to randomization. Participants who report taking chronic clopidogrel also require a 300 mg clopidogrel loading dose unless the investigator can verify that the participant has taken the daily dose for at least the preceding 3 days. Participants who have received dipyridamole or another P2Y12 inhibitor must receive the clopidogrel loading dose after discontinuing the non-clopidogrel P2Y12 inhibitor or dipyridamole/dipyridamole-containing treatment.

i) History of hemorrhage into the brain, subarachnoid hemorrhage, subdural hematoma or spinal cord hemorrhage except cerebral microbleeds (CMB) and minor hemorrhagic transformation of prior infarct manifesting as scattered petechiae (Hemorrhagic Infarction Type 1 [HI1] according to Heidelberg classification).[54]

Note: CMBs are defined as rounded foci of ≤10 mm in size that appear hypointense and distinct from vascular flow voids, leptomeningeal hemosiderosis, or non-hemorrhagic subcortical mineralization on T2* weighted MRI.[55]

j) History of clinically meaningful hepatic disease and/or clinically significant abnormal liver function.

k) Intracranial tumor (except meningioma, which is permitted) or aneurysm >5 mm (except treated aneurysm without history of intracranial bleed, which is permitted) or AVM.

l) History of end-stage renal disease (ESRD) with eGFR <15 mL/min/1.73 m^2, or requiring dialysis.

2) Prior/Concomitant Therapy

a) Any investigational drug or placebo exposure within 4 weeks of study drug administration.

b) Any prior exposure to BMS-986177.

c) Planned use of anticoagulants including warfarin or other vitamin K antagonists, oral thrombin and Factor Xa inhibitors, bivalirudin, hirudin, argatroban, unfractionated and low-molecular-weight heparins, with the exception of heparin or low-molecular-weight heparin (LMWH) used to maintain patency of indwelling catheters. ***Note***: Participants who received UFH or LMWH for DVT prophylaxis prior to enrollment can be randomized. The use of anticoagulants for post-stroke DVT prophylaxis after randomization is prohibited. For post-stroke DVT prophylaxis, non-pharmacological prophylaxis (ie, intermittent pneumatic compression) is recommended.

d) Planned concomitant use of omeprazole or esomeprazole after randomization for the duration of clopidogrel treatment (eg, H2 blockers [except cimetidine] and other PPIs are allowed).

e) Anticipated concomitant chronic (>14 days) use of systemic nonsteroidal anti-inflammatory drugs (NSAIDs). NSAID (including COX-2 inhibitors) use prior to randomization is allowed.

f) Use of combined P-gp and strong CYP3A4 inhibitors or combined P-gp and strong CYP3A4 inducers in the 7 days prior to randomization or the need for ongoing treatment with concomitant oral or intravenous therapy with combined P-gp and strong CYP3A4 inhibitors or combined P-gp and strong CYP3A4 inducers during the study. A list of

combined P-gp and strong CYP3A4 inhibitors is attached as Appendix 11. A list of combined P-gp and strong CYP3A4 inducers is attached as Appendix 12.

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

3) Physical and Laboratory Test Findings

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

- Hemoglobin <9 g/dL
- Platelet count <100,000 mm^3
- aPTT >1.4x upper limit of normal (ULN)
- INR >1.5
- AST or ALT >3x ULN

b) History of or any of the following findings on 12-lead ECG prior to study drug administration.

- Atrial fibrillation or atrial flutter
- Complete heart block or Mobitz second-degree heart block

c) Known positive blood screen for hepatitis C antibody, hepatitis B surface antigen, or HIV-1 and HIV-2 antibody.

Note: Participants with a treated and completely resolved hepatitis C infection without any sequelae are permitted.

4) Allergies and Adverse Drug Reactions

a) History of allergy to BMS-986177, clopidogrel, aspirin, or aspirin-containing compounds.

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

c) History of drug-induced hematologic or hepatic abnormalities.

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated.

Note: Under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Bristol-Myers Squibb approval is required.

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

c) Participants in whom MRI procedures cannot be performed. Section 7.7.2.1 provides a list of some common conditions that may preclude the participants from having MRI. However, this should not be used as a substitute for local clinical standards of care. The ultimate decision to perform MRI in an individual participant rests with the site radiologist, the investigator and the standard set by the local practice.

6) Known SARS-CoV-2 infection within 4 weeks prior to screening.

Note: To be considered for enrollment, symptoms must have completely resolved and based on investigator assessment in consultation with the Medical Monitor/Clinical Trial Physician, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants. Therefore, all participants must fully meet all eligibility criteria.

6.3 Lifestyle Restrictions

Not applicable.

6.4 Screen Failures

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

6.5 Retesting During Screening or Lead-In Period

This study does not permit the re-enrollment of a participant who has discontinued the study as a pre-treatment failure.

Retesting of laboratory parameters and/or other assessments during the screening period will not be permitted except for parameters that require a confirmatory result.

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

7 TREATMENT

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

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

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

7.1 Treatments Administered

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

In this protocol, all Sponsor-supplied treatments (Table 7.1-1) are considered investigational product. The Sponsor will be providing uncoated 100-mg aspirin tablets and clopidogrel 75-mg tablets.

Table 7.1-1: Study Treatments for CV010031

Product Description/ Class and Dosage Form	Potency	IP/Non-IP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
BMS-986177 Capsule	25 mg	IP	Blinded	Blister	Refer to the label on container
BMS-986177 Capsule	100 mg				
Placebo For BMS-986177 Capsule	NA	IP	Blinded	Blister	Refer to the label on container
Clopidogrel Tablets	75 mg	IP	Open-Label	Bottle: North America & South America Blister: Rest of World	Refer to the label on container
Uncoated Aspirin Tablets	100 mg	IP	Open-Label	Blister	Refer to the label on container

7.2 Method of Treatment Assignment

This study will be using an Interactive Response Technology (IRT) to centrally enroll and randomize all participants. Before the study is initiated, each user will receive log in information and directions on how to access the IRT.

During the screening visit, the investigative site will obtain the participant's unique 5-digit participant number from the IRT system. Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with 00001, (eg, 00001, 00002, 00003...00010). The participant identification number (PID) will ultimately be comprised of the site number and participant number. For example, the first participant screened (ie, enrolled) at Site Number 1, will have a PID of 0001 00001. Once it is determined that the participant meets the eligibility criteria following the screening visit, the investigative site will obtain the participant's unique 5-digit participant number from the IRT system.

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

This study initially started with placebo and 6 dose-schedule combination (3 doses x once daily [QD] and twice daily [BID] schedules), with 25% of the participants randomized to placebo. The randomization of participants to the 200-mg BID dose will be considered in a staggered approach after a minimum of 800 participants have been randomized. The DMC will review efficacy and safety data and assess whether it is safe to randomize participants to the 200-mg BID dose group. The target randomization ratio by the end of this study, assuming addition of 200 mg BID, will be 2:1:1:1:1:1 (placebo: 25 mg QD: 25 mg BID: 50 mg BID: 100 mg BID: 200 mg BID). All participants will receive open-label aspirin 100 mg + open-label clopidogrel 300-mg single

loading dose followed by clopidogrel 75 mg once daily (QD) and aspirin 100 mg for 21 days then continue to receive open-label aspirin 100 mg for the duration of the study.

At all study visits when study drug is dispensed, each participant will be assigned a container number by the IRT. Container numbers will be assigned non-sequentially and will correspond to the numbers printed on the packages and bottles containing study drug, and will be recorded on the appropriate electronic Case Report Form (eCRF). The IRT will be available 24 hours per day, 7 days a week.

7.3 Selection and Timing of Dose for Each Participant

Study drug may be administered in the clinical facility or self-administered by the participant or their caregiver at home. Caregivers will need to be properly instructed about study medication dosing requirements by the study staff. The same caregiver should assist the participant with their daily dosing.

Following signing of informed consent, participants will be randomized to receive BMS-986177 or placebo, plus open-label uncoated aspirin 100 mg in combination with clopidogrel (a loading dose followed by maintenance doses) for the next 21 days. Participants will continue treatment from Day 22 through Day 90 with BMS-986177 or placebo, plus open-label 100 mg uncoated aspirin only.

Aspirin and clopidogrel will be given open-label as a background therapy according to the following scenarios:

1) Prior to signing informed consent:
   - Participants who have received a single open-label clopidogrel loading dose of between 300 mg and 600 mg as standard-of-care prior to obtaining informed consent can be enrolled in the study. No additional loading dose of clopidogrel is required for such participants after randomization.
   - Following a standard-of-care clopidogrel loading dose, the standard-of-care clopidogrel daily dose of 75 mg will be taken the next day, and it can be taken prior to randomization.
   - Participants who report taking chronic clopidogrel also require a 300-mg clopidogrel loading dose unless the investigator can verify that the participant has taken the daily dose for at least the preceding 3 days.
2) Prior to randomization and after signing informed consent:
   - Following signing of informed consent, a 300-mg loading dose of clopidogrel and 100 mg aspirin may be assigned for immediate treatment upon consenting the participant and registering the participant in Interactive Response Technology (IRT), if considered clinically appropriate. Daily 75 mg clopidogrel and 100 mg daily aspirin will be started the next day.
3) After randomization:
   - A clopidogrel loading dose of 300 mg along with 100 mg aspirin will be administered after randomization on Day 1 for participants who have not received any clopidogrel loading dose.

- For participants who have received at least 75 mg aspirin as standard of care before randomization, and if this dose was taken on the same day as randomization, then no additional aspirin is required on Day 1. In this case, 100 mg daily aspirin should be started in the morning of Day 2.

The first dose of double-blind study medication (BMS-986177 or placebo) should be taken as soon as possible after the baseline MRI assessment, preferably within 2 hours, but no longer than 6 hours. If outside of the 6-hour post-MRI window, the investigator should call the Medical Monitor for guidance. In instances where the baseline MRI is completed after 48 hours from the onset of the index event, the first dose of study medication should still be taken immediately after randomization and within 48 hours from the onset of the index event.

BMS-986177 or placebo will be taken twice daily (BID), once in the morning (between 6AM - 9AM) and again in the evening (between 6PM - 9PM).

Open-label aspirin and clopidogrel should be taken QD in the morning (between 6AM - 9AM) with the dose of double-blind study medication.

Following the first dose of study medication, the interval between Dose 1 and Dose 2 on Day 1 is flexible to ensure a consistent AM-PM dosing schedule after Day 1 dosing. The second dose of study medication (if outside the window of 6AM - 9AM or 6PM – 9PM) can be administered at a minimum of 6 hours post-dose or maximum of 15 hours post last dose. Three examples are provided below:

- Participant enters the study and is administered study medication at 2:30AM. The next dose of study medication would be administered between 8:30AM and 9AM (a 6- to 6.5-hour window) on the same day. The participant would then receive the next dose between 6PM and 9PM.
- Participant enters the study and is administered study medication at 4AM. The next dose of study medication would be administered between 6PM and 7PM (a 14- to 15-hour window). Since the interval between 4AM and 9 AM is <6 hours, the participant must wait for the evening dose to be taken no more than 15 hours after Dose 1.
- Participant enters the study and is administered study medication at 5PM. The next dose of study medication would be administered between 6AM and 8AM (a 13- to 15- hour window). Since the interval between 5PM and 9PM is <6 hours, the participant would not receive the evening dose and must wait to administer the second dose as a morning dose.

The flexibility in the schedule between Dose 1 and Dose 2 allows the most ethical dosing of BMS-986177 to ensure the integrity of the study while providing appropriate exposure coverage during a high-risk period for a stroke.

Blinded study medication (BMS-986177 or placebo) will be provided by the Sponsor. Open-label aspirin will be provided by the Sponsor. Participants will take one tablet each day in the AM with their morning dose of blinded study medication. Open-label clopidogrel will be provided by the Sponsor. Participants will take one tablet each day in the AM with their morning dose of blinded study medication on Days 1 through Day 21.

Study medication (double-blinded medication and aspirin + clopidogrel) will be provided as a 21 day supply at Day 1 and a 64-day re-supply of double-blind study medication at the Day 21 visit.

The treatment period will last 90 ± 6 days, with the last doses of study medication taken on Day 90 or until the Day 90 MRI visit is completed, but no more than 96 days, while continuing treatment. Participants who cannot complete the Day 90 MRI due to the COVID-19 pandemic should continue treatment with study drug until the MRI is completed and until all other study assessments are completed, if at a later time. For these participants, it is understood that they may not be taking study medication past Day 96 (see Section 9.2.12).

Study medication should be taken at approximately the same time each day once a consistent AM/-PM dosing schedule is achieved. If a participant misses a dose of study medication, the missed dose should be taken as soon as possible and no later than 6 hours after the regular dosing time. If it is greater than 6 hours from the regular dosing time, the missed dose should not be taken. Instead, the next dose should be taken at the regular time. Twice-daily dosing should then be resumed.

7.4 Blinding

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual participant in which knowledge of the investigational product is critical to the participant's management, the blind for that participant may be broken by the investigator. The participant's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual participant's treatment, the investigator should determine that the unblinded information is necessary, i.e., that it will alter the participant's immediate management. In many cases, particularly when the emergency is clearly not related to the investigational product, the problem may be properly managed by assuming that the participant is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The principal investigator should only call in for emergency unblinding AFTER the decision to discontinue the participant's study medication has been made.

For this study, the method of unblinding for emergency purposes is through the IRT system. In case of an emergency, the investigator has unrestricted access to randomization information via IRT and can break the blind through the IRT system without prior approval from the Sponsor. After the unblinding, the investigator shall notify the Medical Monitor or Clinical Scientist. The method of unblinding for emergency purposes is described in the IRT Manual. Participant and unblinded treatment information and the reason for the blind being broken must be recorded on the appropriate study status page of the eCRF.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind. Any request to unblind a participant for non-emergency purposes should be discussed with the Medical Monitor.

A separate analysis team for the Sponsor, separate from the clinical team involved with the conduct of this study, will perform an administrative interim analysis (see Section 10.3.7), in order to facilitate subsequent program development.

Designated staff of Bristol-Myers Squibb Research & Development, not involved in the study, may be unblinded (obtain the randomization codes) prior to database lock to facilitate the bioanalytical analysis of pharmacokinetic samples. A bioanalytical scientist in the Bioanalytical Sciences department of Bristol-Myers Squibb Research & Development (or a designee in the external central bioanalytical laboratory) will be unblinded to (may obtain) the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples, as well as provide assistance for analyses needed for DMC in scope of the DMC charter.

The Data Monitoring Committee (DMC; see Section 5.1.1) will assess safety on an ongoing basis, and will have access to unblinded treatment codes for individual participants. An analysis team, including a reporting statistician and programming support, who are not involved with the conduct of the study, will provide analyses to the DMC.

Except as noted above, other members of Sponsor Research and Development personnel, as well as all vendors responsible for the conduct of the trial (protocol team) will remain blinded.

7.5 Preparation/Handling/Storage/Accountability

The investigational product should be stored in a secure area according to local regulations. The investigator is responsible for ensuring that investigational product is only dispensed to study participants. The investigational product must be dispensed only from official study sites by authorized personnel.

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. Refer to Table 7.1-1 for storage requirements for study medication. If concerns regarding the quality or appearance of the study treatment arise, the study treatment should not be dispensed and contact BMS immediately.

Investigational product documentation (whether supplied by Sponsor or not) that includes all processes required to ensure drug is accurately administered must be maintained. This includes documentation of drug storage, administration and, storage temperatures.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability. Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance. Sites should discuss discrepancies with the participant at each on-treatment study visit.

Each time study medication (BMS-986177, placebo, clopidogrel, or aspirin) is dispensed, compliance will be reinforced. When study medication is returned, compliance will be assessed based upon the participant's interview and a count of the tablets or capsules returned. Compliance should be between ≥80 and ≤120%.

The investigator (or designee) will record the amounts of study medication dispensed and returned at each visit, as well as document reasons for non-compliance in the source document.

The dates of all study medication dosing, including interruptions, missed doses or overdose, must be recorded on the eCRF. Non-compliant participants should be re-educated regarding treatment compliance.

Information on overdose is provided in Section 9.2.8.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

The treatments outlined in the exclusion criteria are prohibited as described below:

- Anticoagulants including warfarin or other vitamin K antagonists, oral thrombin and Factor Xa inhibitors, bivalirudin, hirudin, argatroban, unfractionated and low-molecular-weight heparins, with the exception of heparin or low-molecular-weight heparin (LMWH) used to maintain patency of indwelling catheters.
- Omeprazole or esomeprazole after randomization for the duration of clopidogrel treatment (eg, H2 blockers [except cimetidine] and other PPIs are allowed).
- Chronic (>14 days) use of systemic nonsteroidal anti-inflammatory drugs (NSAIDs). Combined P-gp and strong CYP3A4 inhibitors or combined P-gp and strong CYP3A4 inducers. A list of combined P-gp and strong CYP3A4 inhibitors is attached as Appendix 11. A list of combined P-gp and strong CYP3A4 inducers is attached as Appendix 12.

Medications taken, including statins, anticoagulants and antiplatelet agents, within 7 days prior to randomization must be recorded on the CRF.

No new concomitant medications (prescription, over-the-counter or herbal) are to be administered during study unless they are prescribed for treatment of specific clinical events. Any concomitant therapies must be recorded on the eCRF.

7.7.2 Other Restrictions and Precautions

Participants are not permitted to consume any food or beverages containing grapefruit juice for the duration of the study.

7.7.2.1 Imaging Restriction and Precautions

Study participation does ***not*** require x-ray imaging (eg, computed tomography). Study MRIs may be performed with or without contrast administration as per investigator discretion and local clinical practice.

Imaging contraindications should be considered in this assessment. Participants with tattoos, metallic implants, pacemakers, etc., may be excluded from MRI.

MRI contraindications include, but are not limited to:

1) History of claustrophobia
2) Physical limitation related to fitting in the bore of the magnet (i.e., weight greater than that allowable by the MRI table)

3) MRI-incompatible implantable cardiac device, epicardial pacemaker wires, MRI-incompatible cardiac valve prostheses, and MRI-incompatible vascular clips less than two months old, or MRI-incompatible aneurysm clips of any age
4) MRI-incompatible cochlear implants
5) Spinal nerve stimulator
6) Infusion pump that cannot be discontinued temporarily for the scan
7) Tattoos or permanent makeup near the eye
8) Metallic fragments in the eyes/orbits or in the vicinity of the brain or major neurovascular structures of the body
9) Employment history, which involves exposure to welding; unless absence of metallic fragments is documented by X-ray examination as per institutional practice.
10) Shrapnel at any place in the body

The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the investigator and the standard set by the local Ethics Committee.

7.8 Treatment After the End-of-Study

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

8 DISCONTINUATION OR INTERRUPTION CRITERIA

During the course of the study, situations may occur in which the investigator considers a temporary interruption or permanent discontinuation of study drug necessary. For treatment interruptions ≥48 consecutive hours, the period of interruption should be noted and the investigator should document on the CRF the time and date of interruption and restart of therapy, as well as the reason for interruption and measures taken to correct the event. An adverse event (AE) should be reported, if applicable.

Guidance on dose interruptions or permanent discontinuations for selected events are described below. For an individual participant, dose interruptions may be more or less conservative than indicated below based on the clinical judgment of the investigator.

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 case report form (CRF) page.

8.1 Bleeding

All study treatment must be discontinued immediately in participants with a major bleeding event (BARC Types 3 and 5). Please refer to the Study Events Assessment Manual for definitions/details related to BARC bleeding criteria.

Participants with other than major bleeding or suspected bleeding should be assessed for an underlying cause with appropriate laboratory testing (e.g., hematology, ultrasound, CT, MRI). The date and time of onset of the bleeding event should be recorded on the CRF. Refer to Section 9.2.1 for measures to consider for management of a bleeding event.

8.2 Elevated Liver Function Tests

All participants will discontinue treatment with blinded study treatment immediately if criteria for drug-induced liver injury (DILI) are met (see Section 9.2.11 for details).

In addition, stop treatment with blinded study treatment if:

- ALT and/or AST >5x ULN for ≥7 consecutive days, confirmed by repeat.
- ALT and/or AST ≥10x ULN, confirmed by repeat.

Interrupt treatment with blinded study treatment if:

- ALT and/or AST >3x ULN, confirmed by repeat.

Participants with abnormal liver function tests should be followed until ALT/AST returns to <2x ULN or to baseline prior to considering re-start of treatment with blinded study treatment, but not later than 14 days post-interruption.

8.3 Elective Procedures or Surgery

The anticoagulant effects of BMS-986177 should dissipate in 48 - 72 hours after the last dose of the drug. Therefore, blinded study treatments must be stopped at least 48 hours prior to an invasive procedure to reduce the risk of bleeding. The participant will re-start blinded study medication once the investigator determines that hemostasis is secure and resuming treatment is safe, but no earlier than 24 hours after the procedure/surgery.

The interruption of aspirin or clopidogrel treatment for elective procedures or surgery should follow local practice.

8.4 Emergency Procedures

For participants receiving BMS-986177, the risk of bleeding with invasive procedures is unknown. At therapeutic doses, the anticoagulant effects of BMS-986177 will not be reflected by INR values, but may be reflected by prolongation of aPTT. Currently, there is no reversal agent for BMS-986177. However, the anticoagulant effect of BMS-986177 dissipates in 48 - 72 hours. Refer to Section 9.2.1 for measures to consider for management of a bleeding event.

For participant with a new stroke during the study period, the use of thrombolytic therapy, mechanical thrombectomy (without stenting), or other standard-of-care therapy, is to be implemented at the discretion of the investigator, to include possibility of unblinding (see Section

7.4). If thrombolytic therapy and/or mechanical thrombectomy is used, study treatment with BMS-986177 must be interrupted and restart of BMS-986177 is only permitted if all of the following conditions are met:

- At least 24 hours have elapsed between end of IV thrombolytic use/thrombectomy and first dose of study medication.
- Clinical imaging has been performed to exclude any hemorrhagic transformation of the new infarct.
- Post-thrombolytic therapy/post-thrombectomy INR $\leq$ 1.5, aPTT $\leq$ 1.4 at the time of BMS-986177 restart.
- No contraindications have been identified that in the opinion of the investigator would preclude start of study medication (eg, large infarct volume, procedure-related bleeding).
- All other study criteria are met.

In addition, we recommend following local practice and considering fibrinogen > 150 mg/dL before initiation of study treatment.

8.5 Other Reasons for Permanent Discontinuation from Study Treatment

Participants MUST discontinue BMS-986177 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 should be encouraged 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 or program by Bristol-Myers Squibb (BMS).
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

  Note: Under specific circumstances, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and Sponsor approval is required.
- Severe non-compliance to protocol, as judged by the investigator and/or Sponsor.
- Incorrect enrollment (i.e., the participant does not meet the required inclusion/exclusion criteria) for the study, as determined after consultation with the Sponsor.
- Pregnancy: the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/designee of this event. See Section 9.2.7.

Discontinuation of open-label clopidogrel and/or aspirin are at the discretion of the investigator.

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In the event a female participant becomes pregnant during a clinical trial, the study treatment must be discontinued immediately. Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy. If the investigator determines a possible

favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

All participants who discontinue study treatment should comply with protocol-specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

8.6 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and should be encouraged to continue to be followed for protocol specified follow-up procedures. For these participants, the following visits must be conducted:

- End-of-treatment assessments, except MRI, at the time of study drug discontinuation.
- MRI at Day 90 (± 6 days). In the event that participants are unable or not permitted to attend the Day 90 visit at the study site due to the COVID-19 pandemic, the Day 90 MRI may be performed at an external facility provided that the MRI protocol and scanner have been pre-approved by the central imaging vendor. In the event the Day 90 MRI cannot be performed within the ± 6-day window, the MRI can be acquired at any time after Day 90 using the study site or an external facility MRI scanner. For these participants, it is understood that they may not be taking study medication past Day 96.
- A phone call visit Day 97 ± 2 (7 days after Day 90 MRI)

In addition, a follow-up telephone contact between discontinuation and Day 90 MRI is encouraged for participants who permanently discontinue study treatment early. 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.

For participants who withdraw consent for follow-up, there should be documentation of the reason for withdrawal. Study staff should explicitly seek information about the possible contribution of AEs to the participant's desire to withdraw and document any AEs that are identified in the AE section of the CRF.

Withdrawal of consent for treatment with study medication should be distinguished from withdrawal of consent for follow-up visits, telephone contacts, or medical records checks. Participants requesting withdrawal from follow-up should be informed that withdrawal of consent for follow-up will result in loss of important information about the benefits and risks of BMS-986177.

- 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 collected, 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.

8.7 Post-Study Treatment Follow-up

Post-treatment follow-up is required to assess participant safety and to preserve the integrity of the study. Efficacy outcomes will also be collected during the follow-up period. If study treatment is discontinued early, the participant is expected to complete the end-of-treatment assessments at the time of discontinuation (Table 2-2) except MRI. For these participants, a Day 90 MRI, as well as Day 97 visit, must be completed at the planned visit dates. In the event that participants are unable or not permitted to attend the Day 90 visit at the study site due to the COVID-19 pandemic, the Day 90 MRI may be performed at an external facility provided that the MRI protocol and scanner have been pre-approved by the central imaging vendor. In the event the Day 90 MRI cannot be performed within the ± 6-day window, the Day 90 MRI can be acquired at any time after Day 90 using the study site or an external facility MRI scanner. For these participants, it is understood that they may not be taking study medication past Day 96.

8.8 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 at 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, 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 (see Section 2). Protocol waivers or exemptions are not allowed. All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of informed consent may be utilized for screening or pre-treatment 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

All participants will have a study MRI scan at baseline (Day 1) and Day 90, as described in Table 2-1 and Table 2-2. The baseline MRI should be acquired within 48 hours of the index event and prior to randomization on Day 1. If the baseline MRI cannot be performed within 48 hours of the index event and before randomization, it can be acquired after randomization but must be performed within 72 hours of the index event and up to 24 hours after randomization. If the study-specific MRI cannot be acquired at baseline, a clinical (standard-of-care) MRI scan can be used provided that the clinical MRI protocol and scanner have been pre-approved by the central imaging vendor.

The first dose of study medication (BMS-986177 or placebo) should be taken as soon as possible after the baseline MRI assessment, preferably within 2 hours, but no longer than 6 hours. If outside of the 6-hour post-MRI window, the investigator should call the Medical Monitor for guidance. If the baseline MRI is completed after 48 hours from the onset of the index event, the first dose of study medication should still be taken immediately after randomization within 48 hours from the onset of the index event.

The baseline MRI and the Day 90 MRI will be submitted to a central imaging vendor for analysis. Details regarding MRI acquisition, including required sequences, slice thickness, and qualifying phantom image(s) are presented in the CV010-031 Imaging Manual. Sites must be trained and qualified prior to scanning the first study participant.

9.1.1 Primary Efficacy Assessments

The primary efficacy endpoint assessment is the composite of a new ischemic stroke during the treatment period and new covert brain infarction (FLAIR + DWI) detected by MRI on Day 90.

Please refer to the Study Events Assessment Manual for definitions/details concerning stroke/covert brain infarction endpoints.

9.1.2 Secondary Efficacy Assessments

The following are secondary efficacy assessments:

- Composite of new ischemic non-fatal stroke, non-fatal myocardial infarction, or all-cause death
- Location, number, and volume of new FLAIR + DWI lesions
- National Institutes of Health Stroke Scale (NIHSS), Modified Rankin Scale (mRS), Montreal Cognitive Assessment (MoCA), and Digit Symbol Substitution Test (subtest of WAIS-IV) will be collected at baseline (at randomization for NIHSS), on Days 21 and 90, and at the time of a new stroke event. MoCA and DSST (subset of WAIS-IV) will be read by a third-party central laboratory blinded to treatment.

9.2 Safety Assessments

9.2.1 Bleeding

The main safety endpoint assessment is major bleeding (based on BARC Types 3 and 5 definitions). Participants with bleeding or suspected bleeding will be assessed and treated according to usual clinical practice at each site. Severity of bleeding will be classified according to BARC, ISTH and PLATO (Refer to the Study Events Assessment Manual for definitions and details for the bleeding endpoints).

Approach to a Participant with a Bleeding Event

If a participant has a bleeding event requiring intervention during the study, the following measures should be considered:

- Discontinue the study drug (refer to Section 8.1, Discontinuation of Study Drug).
- Usual treatment measures for bleeding events, including local pressure, fluid replacement and hemodynamic support, and blood transfusion, if indicated
- Other causes besides antithrombotic medication can contribute to the seriousness of the bleeding event (e.g., rule out thrombocytopenia, disseminated intravascular coagulation, and other coagulopathies, kidney and liver dysfunction, concomitant medications, etc.) and should be assessed and treated accordingly
- Consultation with a coagulation/hematology expert
- Possibility of unblinding at the discretion of the investigator (see Section 7.4)

Currently, there is no specific reversal agent for BMS-986177. Before considering the use of any pro-hemostatic agent, the benefit and risk for each individual participant should be assessed, and consultation with a hematologist should be considered. Replacement therapy with Factor XI concentrates is not recommended because the participants are not Factor XI deficient. BMS-986177 does not bind Factor XI but rather only binds to activated Factor XI. Therefore, increasing circulating Factor XI is not likely to have a significant impact on BMS-986177 pharmacology. In vitro studies in human plasma demonstrated that addition of 4-factor activated

prothrombin concentrate complex (FEIBA®, aPCC) or recombinant Factor VIIa (NovoSeven®) reduced the BMS-986177-induced prolongation of the aPTT. In FXI-deficient participants, recombinant Factor VIIa has been used successfully to prevent surgical bleeding without complication. Therefore, if severe bleeding occurs that cannot be controlled by the above measures, or emergent surgery/invasive procedure is required, pro-hemostatic agents may be considered according to their package insert.

At therapeutic doses, the anticoagulant effects of BMS-986177 will not be reflected by international normalized ratio (INR) values but may be reflected by prolongation of aPTT. The anticoagulant effect of BMS-986177 dissipates in 48 to 72 hours after the last dose.

Clopidogrel and aspirin inhibit platelet function and may also contribute to bleeding. Participants receiving clopidogrel and aspirin should be managed according to the local standard-of-care and the drug product label.

9.2.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 3.

AEs will be reported to the investigator 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.

9.2.3 Time Period and Frequency for Collecting AE and SAE Information

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

Section 6 in the Investigator's Brochure[26] (IB) represents the Reference Safety Information (RSI) to determine expectedness of SAEs for expedited reporting. Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs that occur during the screening period through the follow-up period must be collected.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure:

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF section. Labs performed locally for assessment of SAEs should have reports faxed or scanned and emailed to [redacted].

- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of this being available.

Investigators are not obligated to actively seek NSAEs 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 NSAEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

9.2.4 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 NSAE 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.

9.2.5 Follow-up of AEs and SAEs

- Non-serious 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 NSAEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified non-serious AEs must be recorded and described on the NSAE 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.
- Investigators should collect a Medical Release Form from all study participants to allow access to SAE information occurring at off-site medical facilities.

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 8.8).

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

9.2.6 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential to meet legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (e.g., 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 AEs 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.

9.2.7 Pregnancy

If, following initiation of the study treatment it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives (4 days) after product administration, the investigator must immediately notify the Sponsor Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to Sponsor 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. If, for whatever reason, pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant/Sponsor /IRB/EC, as applicable.

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.

9.2.8 Overdose

For this study, the accidental or intentional administration of any dose of BMS-986177 that is considered both excessive and medically important by the investigator will be considered an overdose and should be reported as a SAE (medically important event).

The sponsor does not recommend specific intervention for an overdose. There is no known antidote for overdose with BMS-986177 and no studies have been performed to assess methods of reversing BMS-986177 absorption effects; however, in theory, activated charcoal may reduce the absorption of BMS-986177 if given early after administration of BMS-986177.

See Section 9.2.1 for management of serious bleeding.

Overdose of aspirin or clopidogrel may increase the risk of bleeding. Follow the local product label for management of aspirin or clopidogrel overdose.

In the event of an overdose, the investigator or treating physician should contact the Medical Monitor immediately and:

- Obtain a plasma sample for PK analysis as soon as possible after the last dose of study treatment, if requested, by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing on the CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

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

9.2.9 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the non-serious 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 abnormal laboratory test result that required the participant to have study treatment discontinued or interrupted
- Any abnormal laboratory test result that required the participant to receive specific corrective therapy

The clinical rather than laboratory term (e.g., anemia *vs.* low hemoglobin value) should be used wherever possible by the reporting investigator.

9.2.10 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 NSAE or SAE, as appropriate, and reported accordingly.

9.2.11 Potential Drug Induced Liver Injury (DILI)

Participants meeting the criteria for DILI must have blinded study treatment discontinued immediately.

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 Appendix 3 for reporting details).

Potential drug-induced liver injury is defined as:

ALT or AST elevation >3x ULN

AND

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

AND

No other immediately apparent possible causes of transaminase 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.

9.2.12 Magnetic Resonance Imaging

A baseline and Day 90 MRI of the brain are required for all participants randomized in the trial per study guidelines. All scans should be acquired in compliance with the study-specific MRI protocol as outlined in the imaging manual provided by the central imaging vendor.

The baseline MRI should be acquired within 48 hours of the index event and prior to randomization on Day 1. If the baseline MRI cannot be performed within 48 hours of the index event and before randomization, it can be acquired after randomization but must be performed within 72 hours of the index event and up to 24 hours after randomization. If the study-specific MRI cannot be acquired at baseline, a clinical (standard-of-care) MRI scan can be used provided that the clinical MRI protocol and scanner have been pre-approved by the central imaging vendor.

A second MRI of the brain will be performed on Day 90 ± 6 days (based on randomization on Day 1) to accommodate scheduling and scanner availability. Sites are encouraged to schedule the Day 90 MRI at the time of the baseline visit. All participants should remain on study treatment until the Day 90 MRI is performed up to Day 96.

In case of early study drug discontinuation prior to Day 90, a Day 90 MRI will still be required.

In the event that participants are unable or not permitted to attend the Day 90 visit at the study site due to the COVID-19 pandemic, the Day 90 MRI may be performed at an external facility provided that the MRI protocol and scanner have been pre-approved by the central imaging vendor. In the event the Day 90 MRI cannot be performed within the ± 6-day window, the Day 90 MRI can be acquired outside of the + 6-day window after Day 90 using the study site or an external facility MRI scanner. For these participants, it is understood that they may not be taking study medication past Day 96.

All MRI scans must be performed at qualified MRI facilities. More than one imaging facility can be utilized during conduct of the study with preference to perform baseline and Day 90 scans on the same scanner or of the same manufacturer, or minimally with the same magnet strength as the baseline scan.

An Imaging Manual and Quick Reference Guide (QRG) will be provided detailing site qualification process, required MRI sequences, and participant scanning.

9.2.13 Physical Examinations

A complete physical examination should include general appearance, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdomen, lymph nodes, extremities, neurological, skin, and musculoskeletal. Full physical exams will be conducted at screening and on Day 90.

A brief physical assessment (including organ systems pertinent to the participant's signs, symptoms, or adverse events, e.g., assessment of signs of thromboembolism and bleeding) will be conducted on the Day 21 visit.

Physical measurement of height and weight will also be collected at screening and weight will be collected again on Day 90.

The individual performing the physical examinations must be licensed by state law and must be delegated to conduct this study-specific assessment after randomization.

9.2.14 Vital Signs

Vital signs (blood pressure and heart rate) will be recorded during the screening visit and at each study visit during the treatment period. Vital signs scheduled at the same visit as blood samples or ECG should be completed before blood is drawn.

9.2.15 Electrocardiograms

A 12-lead ECG will be recorded at screening, on Day 21, and at the end-of-treatment visit (Day 90).

9.2.16 Clinical Safety Laboratory Assessments

All screening laboratory tests will be performed locally to assess eligibility per inclusion/exclusion criteria. Laboratory samples collected as standard-of-care prior to signing informed consent can be used to assess eligibility if meeting protocol-specified requirements. Investigators must document their review of each laboratory safety report.

The central laboratory will perform the study-specific analyses and will provide reference ranges for these tests. A central laboratory sample will be collected on Day 1 prior to the first dose of blinded study medication, and at Day 21, Day 60, and Day 90 visits. In the event that the Day 1 lab results are not available, local screening labs will be used for analysis.

Table 9.2.16-1: Clinical Laboratory Assessments

Hematology:	
Hemoglobin	
Hematocrit	
Red blood cell count (RBC)	
Total leukocyte count, including differential	
Absolute platelet count	
Chemistry:	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin (TB) Direct bilirubin (done as reflex if TB is >2x ULN) Alkaline phosphatase Bicarbonate Lactate dehydrogenase (LDH)	Total Protein Albumin Sodium Potassium Chloride Calcium

Table 9.2.16-1: Clinical Laboratory Assessments	
Hematology:	
Creatinine eGFR Blood Urea Nitrogen (BUN) Uric acid	Phosphorus Magnesium
WOCBP Only:	
Pregnancy test (at screening and every 30 days).	
Follicle stimulating hormone (FSH) (screening only for women only) use as applicable	

Note: PT and aPTT are collected as PD markers and will be sent to the central laboratory for analysis (See Section 9.3).

9.3 PK, PD, Biomarkers and PK/PD Assessments

Table 9.3.1.1-1 and Table 9.3.2.1-1 show collection times for PK and PD in participants who are being treated. Samples for BMS-986177 PK are considered mandatory and the planned times allow a window to accommodate site staff and scheduling. PK and PD data will be used for exploratory exposure-response (E-R) analyses for efficacy, safety, and PD endpoints. These samples will be analyzed at central laboratories: PT aPTT and FXI clotting activity assay, and the results will be blinded to investigator, study staff and Sponsor.

9.3.1 PK Assessments

Pharmacokinetics of BMS-986177, clopidogrel (and metabolites), aspirin (acetylsalicylic acid) and its major metabolite (salicylic acid) will be assessed. A population PK model (PPK) will be developed to understand the PK of BMS-986177 (See Section 10.3.4).

9.3.1.1 PK Sample Analyses

The plasma samples will be analyzed for BMS-986177 by a validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) assay. The plasma samples for acetylsalicylic acid, salicylic acid, clopidogrel, and clopidogrel metabolite will be analyzed by validated high-performance liquid chromatography mass spectrometry/mass spectrometry assays. (HPLC-MS/MS). PK samples collected from a participant who received placebo will not be analyzed for BMS-986177, but may be analyzed for clopidogrel (and metabolites), aspirin and salicylic acid. Detailed instructions for the PK blood collection, labeling, processing, storage, and shipping will be provided to the site in the central laboratory procedure manual.

In addition, after the scheduled PK analyses are completed, residual plasma may be used for metabolite profiling or assessment of other metabolites, if the need arises and to the extent possible. If these analyses are conducted, they will be reported separately from the CSR. Further details of sample collection and processing will be provided to the site in the central laboratory procedure manual.

Table 9.3.1.1-1 lists the sampling schedule to be followed for the assessment of PK in treated participants. Further details of blood collection and processing will be provided to the site in the central laboratory procedure manual. In addition to the times listed in the table below, a sample

for measurement of BMS-986177 plasma concentration, PT, aPTT and FXI clotting activity should be collected as close as possible to the time of major bleeding or a new stroke.

Table 9.3.1.1-1: Pharmacokinetic Sampling Schedule

Study Day of Sample Collection	Time of Sample Collection Relative to BMS-986177 Dose (Hour:Min)[a]	BMS-986177 Blood Sample for Plasma	Clopidogrel, Acetylsalicylic Acid and Salicylic Acid Blood Sample for Plasma
Day 1- Day 4 (Relative to 1st or 2nd dose)[b]	00:30 - 6:00	X	
	6:00 - 12:00	X	
	12:00 - 72:00[c]	X	
Day 21	Any time	X	X
Day 90	Any time	X	X[d]
Outcome Event	Up to 48 hours after stroke event or major bleeding event	X	X

a It is critical to record ingestion time of each dose prior to each PK sample and sample collection time. Ensure that there is at least a one-hour gap between samples collected, as windows are continuous.

b All PK samples on Day 1 - Day 4 should be collected relative to the same dose. Select either the first dose or second dose and collect Day 1 - Day 4 samples relative to dose selected.

c For participants discharged prior to this sampling window, collect one PK sample prior to discharge.

d Sample for acetylsalicylic acid and salicylic acid PK only.

9.3.2 PD and Biomarker Assessments

Effects of BMS-986177 on PD markers including aPTT, FXI clotting activity, and PT will be assessed. Blood samples for these PD markers will be collected and sent to central laboratories for analysis. A dose-response assessment will be performed for aPTT and FXI clotting activity as PD biomarkers for BMS-986177 according to the sample collection schedule detailed in Table 9.3.2.1-1.

9.3.2.1 Exploratory Biomarker Assessments

Blood will be drawn at the times indicated in Table 9.3.1.1-1 for exploratory biomarker assessments. The goal of these assessment is to explore the effect of BMS-986177 on the body, explore markers related to the FXI pathway and associated pathways, markers of stroke, thrombosis, cardiovascular disease and related pathophysiological conditions (such as inflammation, endothelial function, metabolic, neurological, and extracellular matrix turnover).

The assessments may include, but are not limited to, those listed below and in Table 9.3.2.1-1 and Table 2-2.

- Thrombosis, hemostasis, and cardiovascular diseases related exploratory biomarkers such as PT, FXI antigen, D-dimer, and F1.2.
- Exploratory serum and plasma biomarkers associated with FXI pathway or pathways impacted by target, stroke, cardiovascular disease, metabolic and neurological disorder, brain injury,

endothelial dysfunction, inflammation, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection status or related pathophysiological pathways. Biomarkers may include but are not limited to kallikrein, bradykinin, IL-6, NT-proBNP, fibrinogen, chemerin, soluble von Willebrand factor (vWF) and or related multi-biomarker panels. Exploratory serum and plasma samples to develop new or improved assays for pathway markers associated with either BMS-986177, FXI, stroke, or cardiovascular diseases.

- A PK/PD sample should be drawn at the time of stroke or major bleed.
- A blood sample for future genotyping may include, but not be limited to specifically FXI, genes related to FXI pathway, stroke, cardiovascular disease, and disposition of BMS-986177 and other co-medication (drug absorption, distribution, metabolism, and excretion related genes such as CYP3A4/CYP3A5, 2C9/2C19, P-gp, MDR1, BCRP, OATP1B1, CES1 and CES2) as well as Whole Genome Sequencing. These samples will be collected only in participants in countries and sites where genetic testing is allowed and who opt in to genetic testing as captured on an Informed Consent Form (ICF).
- Further details of sample collection and processing will be provided to the site in the central laboratory procedure manual. Results of exploratory biomarkers may be reported separately from the CSR.

Table 9.3.2.1-1: Biomarker Sampling Schedule

Study Day of Sample Collection	Time of Sample Collection Relative to BMS-986177 Dose (Hour:Min)[a]	PT, aPTT and FXI Clotting Activity[b]	FXI Antigen	Exploratory Plasma and Serum Biomarkers	F1.2 and DDimer
Day 1- Day 4 (Relative to 1st or 2nd dose)[c]	00:00 (pre-dose)[d]	X	X	X	X
	00:30 - 6:00	X			
	6:00 - 12:00	X			
	12:00 - 72:00[e]	X		X	X
Day 21	Any time	X		X	X
Day 90	Any time	X		X	X
Outcome Event (Up to 48 hours after stroke event or major bleeding event)		X	X		

a It is critical to record ingestion time of each dose prior to each PD sample and sample collection time. Ensure that there is at least a one-hour gap between samples collected, as windows are continuous.

b PD samples (PT, aPTT and FXI clotting activity) must be collected at same time as the matched PK time points, where applicable, and at the time of a new major bleeding or stroke event.

c All PD samples on Day 1 - Day 4 should be collected relative to the same dose. Select either the first dose or second dose and collect Day 1 - Day 4 samples relative to dose selected.

d The pre-dose sample can be collected up to 2 hours before first dose.

e For participants discharged prior to this sampling window, collect one PD sample prior to discharge.

9.3.3 Additional Research Collection

This protocol will include residual sample storage for additional research (AR). All samples, including all residual samples, may be stored and the research with these samples as described in the protocol may continue for 15 years post end-of-study. The scope of work involves using serum, plasma, DNA from whole blood to assess markers of stroke, cardiovascular and associated diseases and pathways (such as inflammation, endothelial function, metabolic, neurological, brain injury, and extracellular matrix turnover). Work may also include studies on the FXI pathway and mechanism of action as well as any pathways impacted by BMS-986177, as well as development of new or improved assays for pathway and markers associated with either BMS-986177, FXI, stroke, or cardiovascular diseases. The goal is to better understand stroke, cardiovascular and associated diseases/syndromes and any effects of the drug, BMS-986177.

Sites in the United States

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

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

For non-US Sites

Additional research is optional for all study participants, except where retention and/or collection of such samples is prohibited by local laws or regulations, ECs, or institutional requirements. Participants (or legally authorized representatives, as applicable) will be required to provide separate informed consent to participate. Participants must also provide separate informed consent to participate in collection of additional blood samples for future genotyping, including, but not limited to FXI. Samples for genotyping will only be collected at sites where allowed by local laws and regulations.

Sample Collection and Storage

All serum, plasma, and blood DNA samples from PK, PD and exploratory biomarker collections (as defined in Table 9.3.1.1-1, Table 9.3.2.1-1 and Table 2-2) may be retained for additional research purposes as described above. Samples kept for future research will be stored at the Sponsor biorepository or an independent, Sponsor-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 15 years after the end of the study or the maximum allowed by applicable law

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

All requests for access to samples or data for additional research will be vetted by the Sponsor to ensure the research supports appropriate research activities.

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, processing, submission and storage are provided in the Study Laboratory Manual.

9.4 Other Assessments

9.4.1 Assessment of Index Stroke and New Strokes

The National Institutes of Health Stroke Score (NIHSS) will be used to assess the index stroke as a qualifying criteria (must be ≤7) at randomization on Day 1. The NIHSS will also be evaluated on Days 21 and 90, and at the time of a new stroke (see Appendix 5).

9.4.2 Assessment of Risk for Subsequent Stroke Associated with Index TIA

The ABCD^2 Score[3] or presence of motor symptoms will be used as one of the qualifying criteria for TIA (must be ≥6) (see Appendix 6).

9.4.3 Assessment of Clinical Severity of Stroke

In participants who have had a prior stroke, the Modified Rankin Scale (mRS) will be used to assess the clinical severity of the prior stroke or TIA at screening as a qualifying criteria (must be ≤3) to be randomized. mRS will also be assessed on Days 21 and 90, and at the time of a new stroke (see Appendix 7).

9.4.4 Assessment of Cognitive Function

Cognitive function will be assessed at baseline on Day 1, on Days 21 and 90, and at the time of a new stroke event by the clinical site and evaluated by a third-party laboratory blinded to study treatment:

- The Montreal Cognitive Assessment (MoCA) (see Appendix 8)
- The Digit Symbol Substitution Test (DSST; subtest of WAIS-IV) (see Appendix 9)

9.4.5 Assessment of Bleeding Severity

Severity of bleeding will be based on definitions contained in the Study Events Assessment Manual for:

- Bleeding Academic Research Consortium (BARC)
- International Society of Thrombosis and Hemostasis (ISTH)
- Platelet Inhibition and Patient Outcomes (PLATO)

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The primary endpoint for this study is the incidence of events within a composite of new ischemic stroke during the treatment period and new covert brain infarction (FLAIR + DWI) detected by MRI at 90 days. Sample size calculations were performed for detecting a dose-response effect with the MCP-MOD methodology using simulations with the Dose-Finding package in R statistical analysis software. Simulations of 2500 clinical trials were performed, assuming a true incidence for placebo of 15%, a plateau shaped dose response relationship with maximum relative risk reduction of 32% for BMS-986177 100 or 200 mg BID relative to placebo and reductions of 10%, 17.5%, and 27% for the 25-mg QD, 25-mg BID, and 50-mg BID doses, respectively. Candidate models included an E_{max} model, a logistic model, and an exponential model.

Using these assumptions, a total of 2100 participants allocated in a 2:1:1:1:1:1 ratio to placebo and BMS-986177, 25 mg QD, 25 mg BID, 50 mg BID, 100 mg BID, and 200 mg BID groups would provide approximately 80% power to demonstrate a dose-response relationship, with a 1-sided type I error of 0.049 (See Section 10.3.7). Without the 200-mg group, a total of 1800 participants allocated in a 2:1:1:1:1 ratio to placebo and BMS-986177, 25-mg QD, 25-mg BID, 50-mg BID, and 100-mg BID groups would provide approximately 79% power to demonstrate a dose-response relationship with similar pattern, but risk reduction of 32% for BMS-986177 50 or 100 mg BID relative to placebo and reductions of 17.5%, and 27% for the 25-mg QD and 25-mg BID doses, respectively. Allowing up to 10% of participants who do not have a clinical event and also do not have a Day 90 imaging assessment, approximately and up to 2350 participants may be randomized. The frequency and reasons for missing data will be evaluated in blinded fashion during the course of the study.

10.2 Populations for Analyses

The analyses will use several populations as defined below:

1) All Enrolled Participants: Includes all participants who signed informed consent.
2) All Randomized Participants /Intent-to-Treat (ITT) Population: Includes all participants who were randomized to a treatment, regardless of whether they received study drug or not. This population will be analyzed according to the treatment assigned at randomization.
3) All Evaluable Participants: Includes All Randomized Participants, as above, excluding those participants' visits where relevant protocol deviations occurred. The relevant protocol deviations will be pre-specified in the SAP prior to database lock.
4) All Treated Participants: Includes all participants who received at least one dose of study medication. This will be the primary population used in safety analyses and will be analyzed according to the treatment assigned at randomization, except in the following cases:
   - If a participant received the same incorrect treatment throughout the study (until either Day 90 or discontinuation of the study drug), then the participant will be analyzed based on the treatment received.

- If a participant received study drug from more than one treatment group, and none of the administrations were consistent with the assigned randomized treatment group, then the participant will be analyzed based on the first treatment received.

5) Pharmacodynamics (PD) Population: A subset of the ITT Population that includes participants with at least one PD endpoint assessed following the first dose of BMS-986177.
6) Pharmacokinetic (PK) Population for BMS-986177, clopidogrel, and aspirin: Includes all participants treated with BMS-986177, clopidogrel, and aspirin, respectively, who also have at least one post-dose PK sample.

The primary efficacy data set will be the ITT population. For the primary efficacy endpoint analysis, the population will include all Randomized Participants who:

- have a primary endpoint event (a new ischemic stroke during the study period or a new covert brain infarction detected by MRI on Day 90)

OR

- have an evaluable MRI image on Day 90.

For the primary endpoint, analysis will be performed using the Evaluable Participant data set as well as the Primary Efficacy data set.

10.3 Statistical Analyses

The Statistical Analysis Plan (SAP) will be developed and finalized before the final 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.

Except as otherwise noted, descriptive summaries will use data from all randomized groups, while dose-response analyses of primary and secondary endpoints will use data from participants randomized to placebo, 25 mg QD and 25 mg, 50 mg, 100 mg, and 200 mg BID groups.

A description of the participant population will be included in the statistical output reported, including subgroups of age, gender, and race.

10.3.1 Demographics and Baseline Characteristics

Frequency distribution and summary statistics for demographic and baseline variables will be presented by treatment group and for all participants combined. Key demographic and baseline variables to be summarized include geographic region, age, gender, race, height, weight, body mass index, vital signs (systolic blood pressure, diastolic blood pressure, and heart rate) and medical history (hypertension, diabetes, heart failure).

10.3.2 Efficacy Analyses

Clinical definitions and details related to the study endpoints can be found in the Study Events Assessment Manual. Table 10.3.2-1 provides details about efficacy endpoints and analysis methods to be used.

Table 10.3.2-1: Efficacy Endpoints and Analysis Methods

Endpoint	Statistical Analysis Methods
Primary • Estimation of dose-response using composite of new ischemic stroke during the treatment period and new covert brain infarction (FLAIR + DWI) detected by MRI at 90 days using central review	Dose-response relationship will be analyzed based on a generalized Multiple Comparisons and Modeling (gMCP-Mod) analysis[56,57] for the BMS-986177 dose regimens, with placebo and 25 mg QD as the lowest dose added to the ordered BID dose regimens. If a dose-response relationship exists, then fitted estimates for the incidence of the primary endpoint will be calculated in each of the treatment groups using the selected dose-response models. An E_{max} model, a logistic model, and an exponential model will be used as the candidate models for the gMCP-Mod analysis.
Secondary • Comparison of rates of the composite of new ischemic stroke during the treatment period and new covert brain infarction (FLAIR + DWI) detected by MRI at 90 days • Event rates for new ischemic non-fatal stroke, non-fatal MI, and all-cause death during the treatment period • Location, number, and volume of new FLAIR + DWI lesions • National Institutes of Health Stroke Scale (NIHSS), Modified Rankin Scale (mRS), Montreal Cognitive Assessment (MoCA), and Digit Symbol Substitution Test (subtest of WAIS-IV) at baseline, on Days 21 and 90, and at the time of a new stroke event.	Point estimates with 95% confidence intervals for the following event rates will be summarized by treatment group. • Composite of new ischemic stroke during the treatment period and new covert brain infarction detected by MRI at 90 days • New covert brain infarction detected by MRI at Day 90 • Composite of new ischemic non-fatal stroke, non-fatal MI and all-cause death during the treatment period • New ischemic stroke during the treatment period • Non-fatal myocardial infarction (MI) • All-cause death Dose-response analysis for new ischemic non-fatal stroke and the composite of new non-fatal stroke, non-fatal MI, and all-cause death will be assessed similar to the primary endpoint analysis. Location, number, and volume of new FLAIR + DWI lesions will be summarized descriptively by treatment group. Functional/disability status assessed by the National Institutes of Health Stroke Score (NIHSS), modified Rankin Scale (mRS), Montreal Cognitive Assessment (MoCA) and Digit Symbol Substitution Test (subtest of WAIS-IV) will be summarized by treatment group.

10.3.3 Safety Analysis

Table 10.3.3-1 provides details about safety endpoints and analysis methods to be used.

Table 10.3.3-1: Safety Endpoints and Analysis Methods

Endpoint	Statistical Analysis Methods
• Major bleeding event rate based on bleeding according to Bleeding Academic Research Consortium (BARC) Type 3 and 5	The event rates of major bleeding (based on BARC Types 3 and 5 definitions) will be summarized by treatment groups and point estimates with 95% confidence intervals will be presented for each treatment group. If a sufficient number of major bleeding events occurs, then dose-response for the BMS-986177 will be assessed.

Table 10.3.3-1: Safety Endpoints and Analysis Methods

Endpoint	Statistical Analysis Methods
• Event rate for all bleeding events, based on BARC, ISTH and PLATO-defined criteria	The event rates for all bleeding will be summarized by treatment group, including point estimates with 95% confidence intervals within group. Additionally, bleeding events will be summarized by BARC category, ISTH (major and CRNM bleeding), and PLATO criteria (major, including life-threatening and other; minor, and minimal).
• Incidence and characteristics of CMBs, hemorrhagic transformation of ischemic stroke and asymptomatic intracranial bleeding on Day 90 MRI	Incidence and characteristics of CMBs, hemorrhagic transformation of ischemic stroke and asymptomatic intracranial bleeding on Day 90 MRI will be summarized by treatment group
• Adverse events, vital signs, physical exams, electrocardiogram (ECG), and clinical laboratory results	• Incidence of adverse events, related adverse events, serious adverse events, adverse events leading to discontinuation, and deaths will be summarized by treatment group Additionally, changes from baseline in vital signs, ECG and clinical laboratory results will be summarized by treatment group.

10.3.4 Pharmacokinetic Analysis

The PK of BMS-986177, clopidogrel (and metabolites), aspirin (acetylsalicylic acid) and its major metabolite, salicylic acid, will be assessed. A population PK model (PPK) will be developed to understand the PK (CL and Vd) of BMS-986177 and the potential effect of covariates (e.g., body weight, age, gender, race, renal function, liver function, concomitant medicine) on the PK of BMS-986177. These results will be reported separately.

10.3.5 Pharmacodynamic and Biomarker Analysis

Percent (%) change from baseline for aPTT, PT and Factor XI clotting activity, as well D-dimer, PT, F1.2, and Factor XI antigen may be summarized by treatment group. In addition, exploratory analyses may be conducted to explore the relationship of BMS-986177 to:

- Percent (%) change from baseline in aPTT and Factor XI clotting activity via exposure-response
- Biomarkers related to FXI pathway, stroke, thrombosis/hemostasis, inflammation and cardiovascular diseases, include, but are not limited to: plasma D-dimer, PT, F1.2, and Factor XI antigen.
- PD and biomarker results and analysis may be reported separately.

10.3.6 Exposure-Response Analyses

Exposure-response analyses will be conducted to explore the relationship of BMS-986177 exposure to the following using data collected from all randomized participants:

- Composite of new ischemic stroke during the treatment period and new covert brain infarction detected by MRI at 90 days
- New ischemic stroke non-fatal MI, and all-cause death during the treatment period

- Major bleeding according to BARC Type 3 and 5 definitions
- Percent (%) change from baseline in aPTT and Factor XI clotting activity
- Biomarkers related to FXI pathway, stroke, thrombosis/hemostasis, inflammation and cardiovascular diseases, including, but not limited to: include, but are not limited to: plasma D-dimer, PT, F1.2, and Factor XI antigen.

10.3.7 Interim Analyses

In order to facilitate subsequent program development, an administrative interim analysis will be conducted after approximately 70% of participants have had a 90 day follow-up. The administrative analysis may include the primary efficacy endpoint, selected secondary efficacy and safety endpoints. An adjustment to the type I error of 0.001 for the final analyses will be done. No changes will be taken with regard to the conduct or analysis of primary or secondary endpoint for this study as a result of this analysis. An analysis team for the Sponsor separate from the clinical team involved with the conduct of this study will conduct the analysis, and unblind data will not be shared outside the analysis group. A Data Monitoring Committee will assess safety throughout the course of this trial (see Section 5.1).

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
$ABCD^2$	neurological assessment scores (age, blood pressure, clinical features,
ACC	American College of Cardiology
ADRC	adaptive design review committee
AE	adverse event
AF	atrial fibrillation
AHA	American Heart Association
ALT	alanine aminotransferase
Am, AM	morning
aPTT	activated partial thromboplastin time
ASA	acetylsalicylic acid
ASO	anti-sense oligonucleotide
AST	aspartate aminotransferase
ALT	amino transaminases
AUC	area under the concentration-time curve
AUC(0-24)	area under the concentration-time curve (time zero to 24 hours post dose)
AVM	arteriovenous malformation
BARC	Bleeding Academic Research Consortium
BID	twice-a-day
BMI	body mass index
BMS	Bristol Myers Squibb
BMS-986177	BMS Factor XIa (FXIa) inhibitor investigational anticoagulant compound
BP	blood pressure
BT	bleeding time
BUN	blood urea nitrogen
C	Celsius
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CL	estimated clearance

Term	Definition
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies
cm	centimeter
Cmax, CMAX	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
COX-2	cyclooxygenase -2, enzyme responsible for inflammation and pain
CRF	case report form (paper or electronic)
CRNM	clinically relevant non-major
CSR	clinical study report
CT	computerized tomography
CTA	computed tomography angiography
CAT	computerized tomography angiography
CV	cardiovascular
CYP	cytochrome P450
CYP3A4	member of the cytochrome P450 family of oxidizing enzymes
DDI	drug-drug interaction
D-Dimer	protein fragment present in the blood after a clot is degraded by fibrinolysis
DILI	drug-induced liver injury
dL	deciliter
DNA	deoxyribonucleic acid
DOAC	direct oral anticoagulants
DSMB	data safety monitoring board
DSST	Digital Symbol Substitution Test
DWI	diffusion-weighted imaging MRI
ECAT	electronically induced thrombus in the carotid artery
EC	ethics committee
EC20	20% of maximal effect is observed
EC50	half maximal effective concentration
EC80	80% of maximal effect is observed
ECG	electrocardiogram
eCRF	electronic case report form

Term	Definition
EDC	electronic data capture
ED90	minimum effective dose in 90% of patients
Emax	asymptotic maximum change from placebo effect
EOT	end of treatment
ESC	European Society of Cardiology
ESRD	end stage renal disease
F1.2	F1.2 fragment of prothrombin
FXa	Factor Xa, one of the enzymes in the coagulation cascade.
FXI (FXI)	Factor XI, one of the enzymes of the coagulation cascade
Factor XIa	Activated plasma Factor XI
FDA	Food and Drug Administration
FIH	first in human
FLAIR	fluid-attenuated inversion recovery
FSH	follicle stimulating hormone
g, gm	gram
GCP	good clinical practice
GPIIb/IIIa	glycoprotein IIb/IIIa
GRE	gradient echo sequences
h	hour
Hb	hemoglobin
HBsAg	hepatitis B surface antigen
HBV, HepB	hepatitis B virus
HCG	human chorionic gonadotropin
HepC	hepatitis C virus
HepB	hepatitis B virus
HepA	hepatitis A virus
HI	hemorrhagic infarction
HIV	human immunodeficiency virus
hr, hrs	hour, hours
HPLC-MS/MS	high-performance liquid chromatography-mass spectrometry/mass

Term	Definition
HR	heart rate
IAC	Imaging Adjudication Committee
IB	Investigator Brochure
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IL-6	interleukin 6
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational Product
IRT	Interactive Response Technology
IRB	Institutional Review Board
IST	international stroke trial
ISTH	International Society on Thrombosis and Hemostasis
ITT	intent to treat
IU	international unit
IUD	intrauterine device
IXRS	interactive web/voice response system
K	slope of the terminal phase of the log concentration-time curve
K3EDTA	potassium ethylenediaminetetraacetic acid
kg	kilogram
λz	terminal disposition rate constant
L	liter
LC-MS/MS	liquid chromatography-mass spectrometry/mass spectrometry
LDH	lactate dehydrogenase
LFT	liver function test
LMWH	low-molecular-weight heparin
Lp-PLA(2)	lipoprotein-associated phospholipase A2

Term	Definition
MACE	major adverse cardiovascular events
MAD	multiple-ascending dose
MCP-Mod	multiple comparison procedures and modeling
MDR1	multidrug resistance protein 1
MED	minimum effective dose
mg	milligram
MI	myocardial infarction
min	minute
mL	milliliter
mmHg	millimeters of mercury
MoCA	Montreal Cognitive Assessment
MRA	magnetic resonance angiography
mRNA	messenger ribonucleic acid
MRI	magnetic resonance imaging (or image)
mRS	modified Rankin Score
µg	microgram
µL	microliter
N	number of participants or observations
N/A	not applicable
ng	nanogram
NIHSS	National Institutes of Health Stroke Score/Scale
nm	nanomolar
NOAEL	no observed adverse effect level
Non-IMP	Non-Investigational Medicinal Product
NSAE	non-serious adverse event
NSAID	nonsteroidal anti-inflammatory drug
NT-proBNP	n-terminal prohormone of brain natriuretic peptide
NVAF	non-valvular atrial fibrillation
NYHA	New York Heart Association
PCR	polymerase chain reaction

Term	Definition
PD	pharmacodynamics
PID	patient identification
[redacted]	
PK	pharmacokinetics
PLATO	Platelet Inhibition and Patient Outcomes
pm, PM	evening
PO	by mouth
PPI	proton pump inhibitor
PPK	population PK(pharmacokinetics)
PT	prothrombin time
PTT	partial thromboplastin time
P2Y12	group of g protein-coupled (gpcr) purinergic receptors
OATP1B1	organic-anion-transporting polypeptide
QC	quality control
QD, qd	once daily
RAR	response adaptive rRandomization
R2	coefficient of determination
RBC	red blood cell
RNA	ribonucleic acid
RRR	relative risk reduction
RSI	reference safety information
SAD	single ascending dose
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SC	Steering Committee
SOP	standard operating procedures
SCTI	Standardized Data Collection for Cardiovascular Trials and Initiatives
SUSAR	suspected, unexpected serious adverse reaction
SWI	susceptibility weighted imaging
TB	total bilirubin

Term	Definition
T-HALF	Half-life
TIA	transient ischemic attacks
ULN	upper limit of normal
Vd	volume of distribution
VTE	venous thromboembolism
VTEp	venous thromboembolism prevention
WOCBP	women of childbearing potential
wt	weight

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

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

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects.

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

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

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

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

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

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

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

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

SOURCE DOCUMENTS

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

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

STUDY TREATMENT RECORDS

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

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • non-study disposition (e.g., lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

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

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance

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

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

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

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

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. Electronic CRF review and approval/signature is completed electronically through the electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

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

MONITORING

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

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site or through other means of remote monitoring approved by the Sponsor and as local regulatory requirements permit, they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents:

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

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

RECORDS RETENTION

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

BMS or designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

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

RETURN OF STUDY TREATMENT

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

If	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the 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 AND PUBLICATIONS

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

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

- National Coordinating Investigator
- Study Steering Committee Chair
- Participant recruitment (e.g., among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (e.g., among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

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

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

ADVERSE EVENTS

Adverse Event Definition:
An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.
Events <u>Meeting</u> 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.
Events <u>NOT</u> 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) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department <24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect

Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [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 9.2.11 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 9.2.7 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 the age of 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

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

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is >40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

Any one of the approved methods of contraception (highly effective and/or less than highly effective) listed below is required during study duration plus 5 half-lives of study treatment BMS-986177 (4 days) plus 30 days (duration of ovulatory cycle) for a total of 34 days

post-treatment completion or after treatment has been discontinued. Local laws and regulations may require use of alternative and/or additional contraception methods.

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

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness
Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of >1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal(coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

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

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until the end of relevant systemic exposure defined as 4 days after the end of treatment plus an additional 90 days for a total of 94 days.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 4 days after the end of treatment with BMS-986177 in the male participant plus an additional 90 days for a total of 94 days.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 4 days after the end of treatment with BMS-986177 plus an additional 90 days for a total of 94 days.

- Refrain from donating sperm for the duration of the study treatment and for 4 days after the end of treatment with BMS-986177 plus an additional 90 days for a total of 94 days.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.7 and the Appendix 3 for Adverse Events and Serious Adverse Events Definitions and Procedures for Evaluating, Follow-up and Reporting

APPENDIX 5 NATIONAL INSTITUTES OF HEALTH STROKE SCALE (NIHSS)

NIH Stroke Scale		
Instructions	**Scale Definition**	**Score**
1a. Level of consciousness: The investigator must choose a response, even if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A "3" is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert; keenly responsive 1 = Not alert, but arousable by minor stimulation to obey, answer, or respond 2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped) 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, areflexic	_____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score "2." Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthia from any cause, language barrier or any other problem not secondary to aphasia are given a "1." **It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.**	0 = Answers both questions correctly 1 = Answers one question correctly 2 = Answers neither question correctly	_____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one-step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness**. If the patient does not respond to commands, the task should be demonstrated to them (pantomime)** and score the result (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly	_____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored but calorie testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be "1." If a patient has an isolated peripheral nerve paresis (CN, III, IV or VI) score a "1." Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness or other disorder of visual acuity or fields should be tested with reflexive movements and a choice made by the investigator. Establishing eyes contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = Normal 1 = Partial gaze palsy. This score is given when gaze is abnormal in one or both eyes, but where forced deviation or total gaze paresis are not present 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver	_____
3. **Visual:** Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat as appropriate. Patient must be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrant anopia is found. If patient is blind from any cause, score "3." Double simultaneous stimulation is performed at this point**. If there is extinction, patient receives a "1" and the results are used to answer question #11.**	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia (blind, including cortical blindness)	_____

(Continued)

NIH Stroke Scale - Continued

4. Facial Palsy: Ask, or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barrier obscures the face, these should be removed to the extent possible.	0 = Normal symmetrical movement 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling) 2 = Partial paralysis (total or near total paralysis of lower face) 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)	_____
5 & 6. Motor Arm and Leg: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder or hip may the score be "9" and the examiner must clearly write the explanation for scoring as a "9".	0 = No drift, limb holds 90 (or 45) degrees for full 10 seconds 1 = Drift, Limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support 2 = Some effort against gravity, limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity 3 = No effort against gravity, limb falls 4 = No movement 9 = Amputation, joint fusion explain:_____ 5a. Left Arm…… 5b. Right Arm……	 _____ _____
	0 = No drift, leg holds 30 degrees position for full 5 seconds. 1 = Drift, leg falls by the end of the 5 second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity, leg falls to bed immediately. 4 = No movement 9 = Amputation, joint fusion explain:_____ 6a. Left Leg…… 6b. Right Leg……..	 _____ _____
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, insure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion may the item be scored "9", and the examiner must clearly write the explanation for not scoring. In case of blindness test by touching nose from extended arm position.	0 = Absent 1 = Present in one limb 2 = Present in two limbs	_____
8. Sensory: Sensation or grimace to pin prick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas [arms (not hands), legs, trunk, face] as needed to accurately check for hemisensory loss. A score of 2, "severe or total," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will therefore probably score 1 or 0. The patient with brain stem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic score 2. Patients in coma (item 1a=3) are arbitrarily given a 2 on this item.	0 = Normal; no sensory loss 1 = Mild to moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected s side; or there is a loss of superficial pain with pinprick but patient is aware he/she is being touched 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm and leg	_____

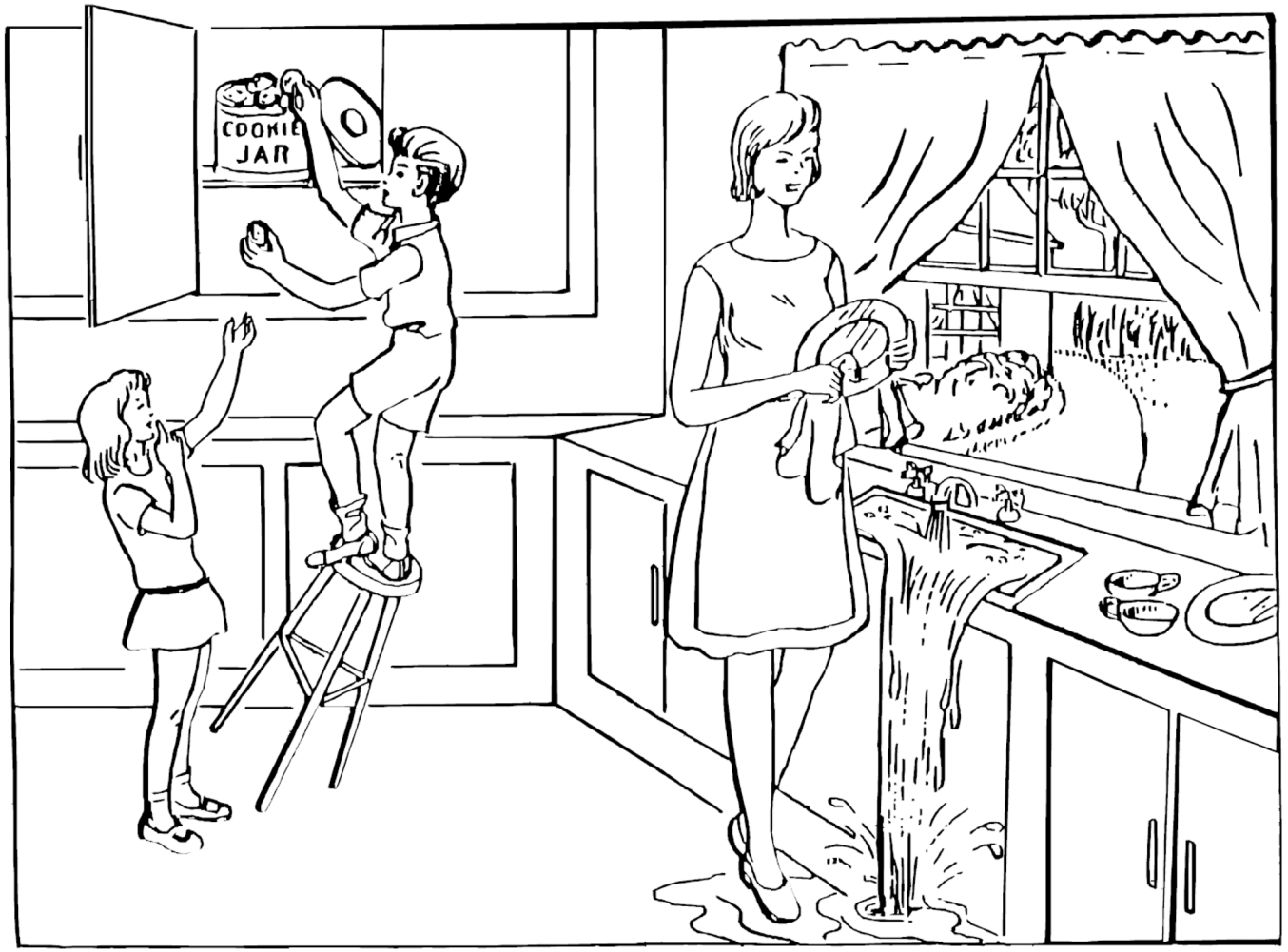
NIH Stroke Scale - Continued

9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. The patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences. Comprehension is judged from responses here as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in coma (question 1a=3) will arbitrarily score 3 on this item. The examiner must choose a score in the patient with stupor or limited cooperation but a score of 3 should be used only if the patient is mute and follows no one step commands.	0 = No aphasia, normal 1 = Mild to moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided material difficult or impossible. For example in conversation about provided materials examiner can identify picture or naming card from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension	_____
10. Dysarthria: If patient is thought to be normal an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barrier to producing speech, may the item be scored "9", and the examiner must clearly write an explanation for not scoring. Do not tell the patient why he/she is being tested**.**	0 = Normal 1 = Mild to moderate; patient slurs at least some words and, at worst, can be understood with some difficulty 2 = Severe; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric 9 = Intubated or other physical barrier, explain	_____
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglector anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = No abnormality 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneousstimulation in one of the sensory modalities 2 = Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognize own hand or orients to only one side of space.	_____
	Total NIHSS Score:	

Time of NIHSS Assessment:_____

Date of NIHSS Assessment:_____

Physician/NIHSS Certified Individual Signature:_____


COOKIE
JAR

You know how

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.

MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

http://www.strokecarenow.com/wp-content/uploads/NIH_Stroke_Scale_with_picture__word_tools.pdf

APPENDIX 6 ABCD^2 SCORE ASSESSMENT TOOL

ABCD^2 Score

The ABCD^2 score is a risk assessment tool designed to improve the prediction of short-term stroke risk after a transient ischemic attack (TIA). The score is optimized to predict the risk of stroke within 2 days after a TIA, but also predicts stroke risk within 90 days. The ABCD^2 score is calculated by summing up points for five independent factors.

Risk Factor	Points	Score
Age		
≥ 60 years	1	☐
Blood pressure		
Systolic BP ≥ 140 mm Hg *OR* Diastolic BP ≥ 90 mm Hg	1	☐
Clinical features of TIA (*choose one*)		
Unilateral weakness with or without speech impairment *OR*	2	☐
Speech impairment without unilateral weakness	1	
Duration		
TIA duration ≥ 60 minutes	2	☐
TIA duration 10-59 minutes	1	
Diabetes	1	☐
***Total ABCD*^{2} score**	0-7	☐

http://www.stroke.org/sites/default/files/resources/tia-abcd2-tool.pdf

APPENDIX 7 MODIFIED RANKIN SCORE

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0–6): _____

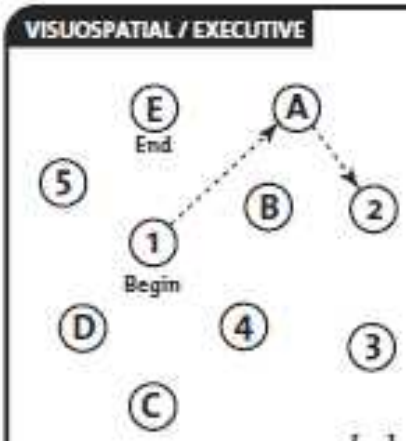
http://www.strokecenter.org/wp-content/uploads/2011/08/modified_rankin.pdf

APPENDIX 8 MONTREAL COGNITIVE ASSESSMENT (MOCA)

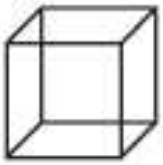
MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE



Copy cube



[ ] [ ]

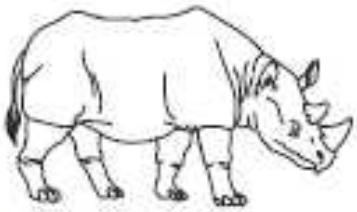
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

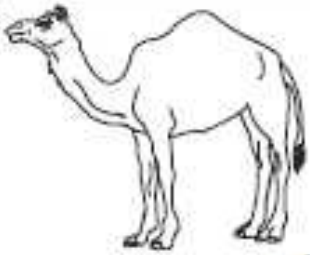
POINTS __/5

NAMING

[ ]



[ ]



[ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt

__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words)

__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train = bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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www.mocatest.org

Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

APPENDIX 9 WAIS-IV DSST CODING SUBTEST

10. Coding

Using a key, the examinee copies symbols that are paired with numbers within a specified time limit.

Materials

Administration and Scoring Manual

Record Form

Response Booklet 1

#2 Pencil Without Eraser

Stopwatch

Coding Scoring Template

Start

Ages 16–90: Demonstration Items, Sample Items, then Test Items

Discontinue

Discontinue after **120** seconds.

Timing

The time limit for the subtest is 120 seconds.

Accurate timing is essential. Begin timing after saying the last word of instruction. Stop timing when the examinee completes all the items or the time limit has expired.

General Directions

- Ensure the examinee has a smooth work surface.
- Use the demonstration items to explain and illustrate the task to the examinee, then allow the examinee to practice by completing the sample items. If the examinee appears confused, repeat the explanation and demonstrate the task again, using the sample items. Proceed with the test items only when the examinee understands the task.
- If a left-handed examinee partially blocks the key with his or her left hand while completing the sample items, stop the administration. Place an extra Response Booklet, opened to the Coding subtest, to the right of the examinee's Response Booklet. Position it so the extra key is aligned with the key the examinee's hand is blocking. Have the examinee complete the remaining sample items using the extra key, so he or she will be accustomed to the arrangement when completing the test items.

- Do not discourage an examinee from making spontaneous corrections unless he or she does so repeatedly and it impedes performance.
- Do not provide the examinee with an eraser. If the examinee asks what to do if he or she makes a mistake, say, **That's OK. Just keep working as fast as you can.**
- If the examinee omits an item or begins to complete a row in reverse order (from his or her right to left), say, **Do them in order. Don't skip any.** Point to the first omitted item and say, **Do this one next.**
- Provide no further assistance on this subtest except to remind the examinee to continue until told to stop (if necessary).

Score

- If the examinee completes all of the test items before the 120-second time limit expires, stop timing and record the completion time in seconds on the Record Form.
- If the examinee does not complete all of the test items within the time limit, record the completion time as 120 seconds.
- Use the Coding Scoring Template to score the examinee's responses. Align the template so that the correct responses are above the examinee's responses. Each test-item number is indicated on the scoring template.
- A response is scored as correct if it is correctly drawn, or if drawn imperfectly, it is clearly identifiable as the keyed symbol. The marks do not need to be identical to the keyed symbol but must be clearly distinguishable from other symbols.
- Score 1 point for each correctly drawn symbol completed within the time limit.
- Score 1 point if the examinee, after realizing a mistake, spontaneously draws the correct symbol next to or on top of the incorrect response.
- Do not include responses to the sample items in the examinee's score.
- Items that the examinee did not attempt (either skipped or did not reach before the time limit expired) should not be counted.
- If the examinee is unable to complete any items, enter a total raw score of 0.
- The total raw score is the number of correctly drawn symbols completed in 120 seconds.

Maximum Coding Total Raw Score: 135 points

Item Administration

16–80 Demonstration Items

The Coding subtest is on the back of the Response Booklet (page 8). Turn the Response Booklet over so the Coding subtest is visible and place it in front of the examinee. Ensure that the examinee sees only Coding. Point to the key at the top of the page and say, **Look at these boxes. Each box has a number in the top part** (point across the numbers from 1 to 9) **and a special mark in the bottom part** (point across the symbols). **Each number has its own mark** (point to 1 and its symbol, then to 2 and its symbol).

Point to the demonstration items and say, **Down here, the boxes have numbers in the top parts but are empty in the bottom parts. You are to draw the marks that belong in the empty boxes, like this.**

Point to the first demonstration item (6) and say, **Here is a 6. The 6 has this mark** (point to the key to show its corresponding symbol), **so I draw that mark in the box, like this** (write the symbol).

Point to the second demonstration item (8) and say, **Here is an 8. The 8 has this mark** (point to the key to show its corresponding symbol), **so I draw that mark in the box** (write the symbol).

Point to the third demonstration item (3) and say, **Here is a 3. The 3 has this mark** (point to the key to show its corresponding symbol), **so I draw that mark in the box** (write the symbol).

Proceed to Sample Items.

Sample Items

Hand the examinee a #2 pencil without an eraser and say, **Now you do these** (point to the sample items). **Stop when you get to this line** (point to the heavy line that separates the sample items from the test items).

Allow the examinee to work alone on the remaining sample items. If a left-handed examinee partially blocks the key with his or her left hand while completing the sample items, stop the administration. Place an extra Response Booklet, opened to the Coding subtest, to the right of the examinee's Response Booklet. Position it so the extra key is aligned with the key the examinee's hand is blocking. Have the examinee complete the remaining sample items using the extra key, so he or she will be accustomed to the arrangement when completing the test items.

If the examinee completes the sample items correctly, offer praise such as **Yes** or **Right** and, finally, **Now you know how to do them.**

If the examinee makes a mistake on a sample item, correct the error immediately. Use the item to review the use of the key. Continue to help the examinee, if necessary, until the examinee correctly completes the sample items. Use explanations such as **You see, this is a 9. The 9 has this mark, so I draw that mark in the box** (write the symbol).

Do not proceed with the test items until the examinee understands the task. If it is clear that the examinee will not be able to understand the task with further instruction, discontinue the subtest.

When the examinee has successfully completed the sample items, proceed to Test Items.

16–90 Test Items

Say, **When I say go, do these the same way. Start here** (point to the first test item), **go in order, and don't skip any. Work as fast as you can without making mistakes until I tell you to stop. Are you ready?**

Explain further if necessary, then say, **Go.** Begin timing and allow 120 seconds.

If necessary, remind the examinee to go in order and continue working. Give no further assistance.

If the examinee is still working at 120 seconds, stop timing and say, **Stop.** Record the completion time as 120 seconds.

Remove the Response Booklet and pencil from the examinee's view before proceeding to the next subtest.

Coding

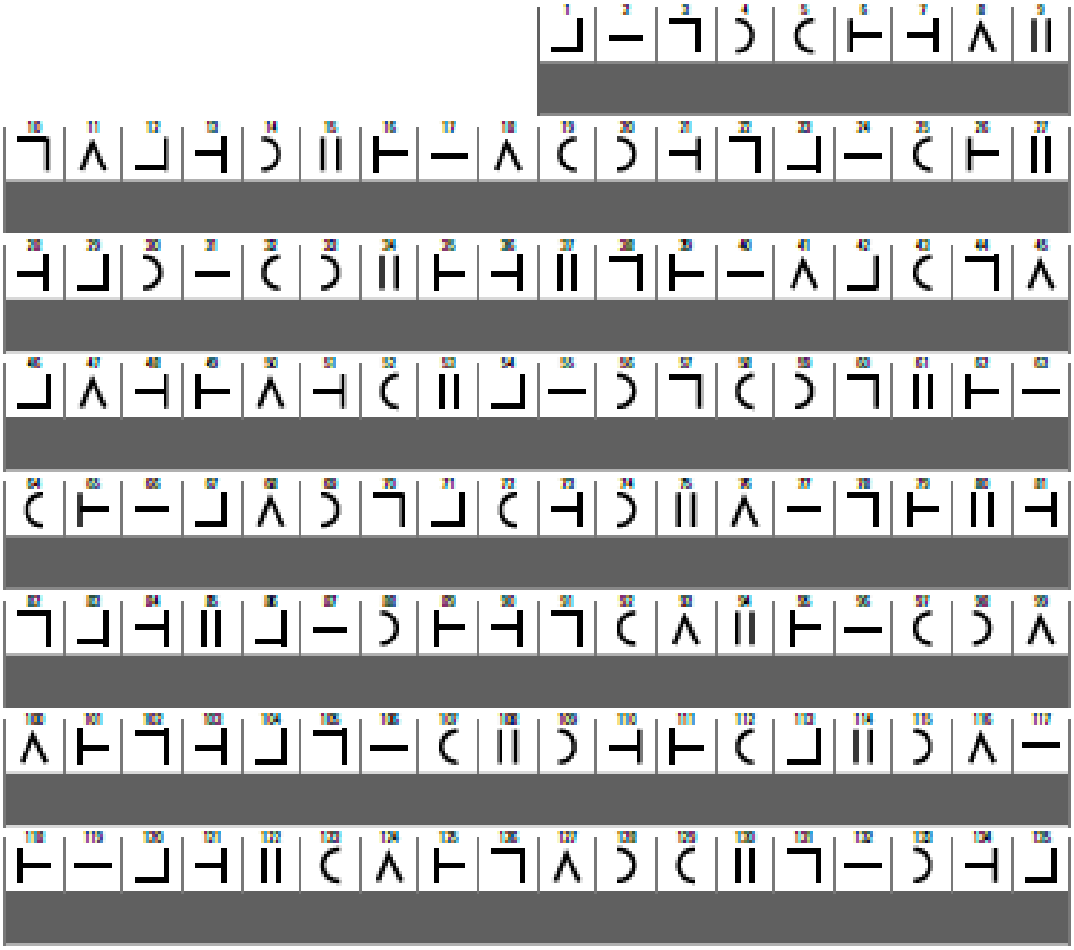
Demo			Sample														
6	8	3	9	5	4	1	7	2	1	4	8	2	7	6	9	3	5
8	3	1	9	2	5	6	4	3	7	2	9	8	1	4	7	6	5
9	1	2	4	7	2	5	6	9	5	8	6	4	3	1	7	8	3
1	3	9	6	3	9	7	5	1	4	2	8	7	2	8	5	6	4
7	6	4	1	3	2	8	1	7	9	2	5	3	4	8	6	5	9
8	1	9	5	1	4	2	6	9	8	7	3	5	6	4	7	2	3
3	6	8	9	1	8	4	7	5	2	9	6	7	1	5	2	3	4
6	4	1	9	5	7	3	6	8	3	2	7	5	8	4	2	9	1

WAIS-IV

Coding Scoring Template

PEARSON PsychCorp

ISBN 015-8980-92-1
9 780158 980928



APPENDIX 10 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for Revised Protocol 05, 24-Aug-2019

The purpose of revised protocol 05 is to simplify the study design while maintaining scientific rigor to attain trial objectives, minimize the number of study participants being exposed to the new investigational drug, reduce the burden on participants and study centers, and streamline study procedures. Specifically, randomization to the once-daily (QD) arms of 50-, 100- and 200-mg dose arms will be closed for the study while maintaining the 25-mg QD arm and twice-daily (BID) dose arms (25, 50, 100, and 200 mg). Assessment of dose response remains the primary objective. The methodology to achieve this will result from analysis of data from placebo, 25 mg QD arms, and BID dose arms (25, 50, 100, and 200 mg) using MCP-MOD to assess dose response, which allows assessment of multiple different dose-response patterns. With fewer study arms primarily focused on one schedule, the selected randomization is more closely oriented to assessment of the overall dose-response relationship with some improved power for detection of a dose-response (from ~77-78% to 80%). The modification of the randomization to a non response-adaptive randomization will be completed while the study is still in the initial "burn-in" period, ie, prior to addition of the 200-mg doses and prior to when the response-adaptive randomization was to be initiated. Participants who have received 50-mg and 100-mg QD doses will continue treatment until they complete the study period. Data acquired in these subjects will be used for descriptive analyses, population PK/PD modeling, and exposure-response analysis.

Maintaining the 25-mg QD dose is of importance in this secondary stroke prevention (SSP) trial for several reasons: 25 mg QD represents the lowest total daily dose included in the study and thus presents unique information in the context of dose-response compared to 50, 100, or 200 mg QD; also, PK/PD modeling with assumptions around combination dual antiplatelet therapy and existing data from direct oral anticoagulants (DOACs) suggests there is potential for this dose of BMS-986177 to be efficacious in secondary stroke prevention with a potential for lower risk of bleeding. The dose change will not allow a separate dose-response assessment for QD; however, it is possible a QD dose can still be an option for Phase III based on modeling and simulation. The 25 mg QD dose plus the four BID doses will still be utilized in the exposure-response assessment. Population PK/PD analysis and exposure-response outcome modeling will be performed using data from all randomized participants, including those who received 50 or 100 mg QD, to support the modeling.

The changes made to the protocol have no adverse impact on the safety or the benefit-risk of the trial participants. Due to the reduction in sample size, fewer patients will be exposed to the new investigational medicine. The safety surveillance performed by the DMC and the Sponsor remains unchanged. The staggered approach for adding the highest 200-mg BID dose remains, ie, the DMC will review the efficacy and safety data including lab-testing data and MRI data from approximately 450 patients who complete 21-day treatment, and will assess benefit and risk of BMS-986177 and make recommendations as to whether or not the 200-mg BID dose can be added.

The table below highlights the key changes made to the protocol.

Sections in the synopsis have been updated to align with the protocol section changes listed below.

Summary of Key Changes for Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	A Global, Phase 2, Randomized, Double-Blind, Placebo-Controlled, Response-Adaptive Dose-Ranging Study of BMS-986177, an Oral Factor XIa Inhibitor, for the Prevention of New Ischemic Stroke or New Covert Brain Infarction in Patients Receiving Aspirin and Clopidogrel Following Acute Ischemic Stroke or Transient Ischemic Attack (TIA) Title Changed to: A Global, Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of BMS-986177, an Oral Factor XIa Inhibitor, for the Prevention of New Ischemic Stroke or New Covert Brain Infarction in Patients Receiving Aspirin and Clopidogrel Following Acute Ischemic Stroke or Transient Ischemic Attack (TIA)	The title was changed to reflect changes in the randomization schema.
Section 2 (Schedule of Activities), Table 2-1 (Screening Period Procedural Outline), Section 9.4.1(Assessment of Index Stroke and New Strokes)	National Institute of Health Stroke Scale (NIHSS) score assessment is removed from screening table and clarified in Section 9.4.1. Added text to Clinical Laboratory Tests Row: “Results from the screening labs should be faxed or scanned to [redacted].”	Neurological impairment will be assessed prior to randomization but not at screening. Clarification for sites.

Summary of Key Changes for Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.2.1 (Phase 1 and 2a Studies with BMS-986177) Table 3.2.1-1 (Highlights of Clinical Pharmacology after Oral Administration of Single and Multiple Doses of BMS-986177 to Healthy Participants and Subjects with Renal or Hepatic Impairment), Section 5.4.2 (BMS-986177 with Aspirin + Clopidogrel)	Added Hepatic Impairment PK properties to the table. Added study results for drug interaction study with BMS-986177 with and without clopidogrel and aspirin.	Provide new preliminary data from recently completed studies.
Section 4 (Objectives and Endpoints), 10.3.2 (Efficacy Analysis)	Kept estimation of dose response but removed specific mention of MED and ED90 in the primary objective. Primary analysis will be based on an MCP-MOD method. Also clarified MRI assessment of endpoint.	MED and ED90 are specific parts of a dose-response relationship. With scientific interest in the overall dose-response relationship, the objective was made more general. Primary analysis to be made consistent with study design, including powering of study.

Summary of Key Changes for Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1 (Overall Design), 5.4 (Scientific Rationale for Adaptive Study Design), 7.2 (Method of Treatment Assignment), 7.4 (Blinding), 10.1 (Sample Size), 10.2 (Randomization), 10.3 (Statistical Analyses), 10.3.6 (Exposure-Response Analyses),10.3.7 (Interim RAR Analyses)	Removed reference to response adaptive randomization (RAR), including interim analyses, including removal of Early Stopping Rules in Section 5.1 (Overall Design, Follow-up Period), removal of Section 5.4 (Scientific Rationale for Adaptive Study Design), removal of Section 10.2 (Randomization). Updated the study schematic to reflect the new dose arms. Removed references to dose arms for 50 mg QD, 100 mg QD, and 200 mg QD BMS-986177, except to note how participants randomized to these arms are included in analyses. Added administrative interim analysis.	To simplify the study design while maintaining scientific rigor to attain trial objectives, minimizing the number of study participants being exposed to the new investigational drug, reducing the burden on participants and streamlining study procedures.
Section 5.2 (Participants), 10.1 (Sample Size)	Sample size was adjusted to indicate 2100 participants will be needed for assessment of dose response, and allowing approximately and up to 2350 participants to be randomized, with consideration of missing data.	Power was raised from approximately 80% (77%-78%) to 80%. Sample size also reflects changes in treatment arms used for dose response (removal of 50-, 100-, and 200-mg QD arms, and keeping 25 mg QD as the lowest dose in the dose-response assessment), as well as modification to a non-RAR design using MCP-MOD analysis method.
Section 5.4.1 (Identification of Effective Doses of BMS-986177)	Doses to achieve trough concentration targets were updated to 50-200 mg QD and 25-100 mg BID.	Review of new pharmacokinetic modeling and simulation data indicated the doses should be revised. Because of the potential effectiveness of 25 mg BID, the 25-mg QD dose was included as the lowest dose in the dose-response assessment.

Summary of Key Changes for Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.3 (Selection and Timing of Dose for Each Participant)	Added another example to demonstrate flexible interval to ensure consistent AM-PM dosing schedule.	To ensure consistent AM-PM dosing schedule if outside the specified window.
Section 9.2.8 Overdose, Appendix 3 Appendix 3 Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow UP and Reporting	Text was revised for reporting overdose as an AE to align with Janssen process.	To provide consistency across protocols with a more conservative approach to capturing AEs. To align with Janssen as they hold the database for the study.
Section 9.3.2.1 (Exploratory Biomarker Assessments), Table 9.3.2.1-1 (Biomarker Sampling Schedule), Section 9.3.3 (Additional Research Collection)	Removed RNA and miRNA sample collection and testing.	These markers are removed to reduce burdens for the participants and the study sites. They are exploratory and are not critical data for the assessment of efficacy and safety of BMS-986177.

Overall Rationale for Revised Protocol 04, 03-May-2019

[redacted] The only change implemented in this revised protocol is to exclude participants with arteriovenous malformation (AVM).

No objectives or endpoints have been changed from the original protocol. The table below highlights the changes made to the protocol.

Summary of Key Changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2: Schedule of Activities, Table 2-1	Included AVM as exclusionary pathology that could account for index symptoms.	To restrict enrollment of patients with the incidental imaging finding of AVM [redacted]
Section 6.2: Exclusion Criteria 1d and 1k and Synopsis: Key Exclusion Criteria 4 and 12		

Overall Rationale for Revised Protocol 03, 05-Apr-2019

The purpose of this amendment is to update the protocol in consideration of feedback from the study sites, Steering Committee, and regulatory agencies. Key changes include: allowance of clopidogrel loading doses of 300 mg to 600 mg prior to signing of informed consent; removal of aortic arch atheroma >4 mm in thickness from vascular imaging criteria; clarifying that MRI is not required to determine study eligibility; clarifying Day 1, pre-dose assessments to be completed, adding instructions for missed doses; providing guidance for the management of bleeding events; modification of the PK and PD sample collection window for the 12-hour post-first dose time point and the requirement of a 12- and 24-hour PK/PD sample collection for TIA subjects on Day 1; and change in the SAE collection duration after discontinuation of study medication. Additionally, new appendices were added for strong CYP3A inhibitors and inducers. An exploratory objective was added to assess the incidence and characteristics of cerebral microbleeds (CMBs), hemorrhagic transformation of ischemic stroke and asymptomatic intracranial bleeding on Day 90 MRI.

No primary or secondary objectives or endpoints have been changed from the original protocol. Other changes are administrative changes that do not impact the integrity of the study, such as typographical errors or clarifications and changes in terminology. The changes made in the body of the protocol were also implemented in the Synopsis, where applicable. The table below highlights the key changes made to the body of the protocol starting at Section 2.

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2: Schedule of Activities, Table 2-1 and Section 5.1	Changed the clopidogrel loading dose from 300 mg to 300 mg to 600 mg when administered as standard-of-care prior to the signing of informed consent	To allow for regional or institutional practices for clopidogrel loading dose
	Removed AVM as exclusionary pathology	To allow for enrollment of patients with the incidental imaging finding from an asymptomatic AVM.
	Removed aortic arch atheroma >4 mm as vascular imaging criteria	To simplify the criteria used for the required evidence of large vessel atherosclerosis on vascular imaging, as an isolated aortic arch atheroma is a rare imaging finding and therefore not routinely assessed with CTA/MRA or other modalities after TIA/stroke
	Added clarification that pre-morbid mRS should be ≤3 prior to index event	To align eligibility criteria for TIA and stroke patients

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Clarified timing of sample collection for clinical laboratory tests prior to treatment	To provide clear instructions on the collection of pre-treatment safety laboratory blood samples for safety monitoring
	Removed T1 and T2 sequences from Study-specific MRI requirements	To clarify that the T1 and T2 sequences are not part of the study-specific MRI protocol.
Section 2: Schedule of Activities, Table 2-2	Changed the clopidogrel loading dose from 300 mg to 300 mg to 600 mg when administered as standard-of-care prior to the signing of informed consent	To allow for regional or institutional practices for clopidogrel loading dose.
	Clarified that NIHSS must be ≤5 at time of randomization	To ensure the safety of study subjects in case of potential fluctuations in the NIHSS between screening and randomization.
	Clarified footnote for required assessment for subjects who have study drug discontinued	To provide further guidance to sites regarding required study related activities in the case of early treatment discontinuation.
	Changed Day 97 visit description from Study Discharge to End-of Study	To align with text
	Added window (±6 days) to Day 90 Visit in header	Added for consistency with text
	Modified required duration of SAE collection from 30 days to 7 days	Modified to coincide with BMS-986177 half-life
Section 3.2.1: Phase 1 and 2a Studies with BMS-986177, Table 3.2.1-1	Updated table to include renal clearance and effect of renal impairment on BMS-986177 PK	Updated PK characteristics to provide results from renal impairment study
Section 4: Table 4-1: Objectives and Endpoints for CV010031	Added new exploratory objective to assess effect of BMS-986177 on characteristics of cerebral microbleeds (CMBs), hemorrhagic transformation of ischemic stroke and	To increase understanding of BMS-986177 safety profile

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	asymptomatic intracranial bleeding on Day 90 MRI	
Section 5.1: Overall Design, Screening Period	Added assessments to be done at screening	Added to align with Schedule of Activities (Table 2-1)
Section 5.1: Overall Design, Double-Blind Treatment Period	Removed vital signs, ECG, PK sample collection and medical history from Day 1, pre-dose assessments	Removed to align with Schedule of Activities (Table 2-2)
	Clarified assessments for participants who permanently discontinue study treatment early	To clarify that this is to be for subjects who permanently discontinue study treatment and not for dose interruptions
	Added clarification that early discontinuation of study medication should be distinguished from withdrawal of informed consent for follow-up	To clarify that participants who discontinue study treatment should continue study assessments unless they also withdraw informed consent
Section 5.1: Overall Design, Early Stopping Rules	Modified probability (RRR> 0.20) from <0.05 to <0.10 for stopping the study early for futility	Corrected to align with RAR report
Section 5.2: Participants	Updated to reflect additional countries and sites	Updated to current operational status
Section 6.1: Inclusion Criteria and Synopsis	Clarify that MRI is not required to determine study eligibility	To also allow subjects to be enrolled in the study based on CT imaging (consistent with accepted alternate modalities to detect ischemic stroke) to reduce the site and subject burden within the randomization window.
	Clarified that NIHSS must be ≤5 at time of randomization	To ensure the safety of study participants in case of potential fluctuations in the NIHSS between screening and randomization.

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Removed aortic arch atheroma >4 mm as vascular imaging criteria and added criteria related to severity of atherosclerotic plaque	To simplify the criteria used for the required evidence of large vessel atherosclerosis on vascular imaging, as an isolated aortic arch atheroma is a rare imaging finding and therefore not routinely assessed with CTA/MRA or other modalities after TIA/stroke
	Added requirement that pre-morbid mRS must be ≤3 before the index event for TIA patients	To align the eligibility criteria for TIA and stroke patients
	Revised total duration of contraceptive use for males who are sexually active with WOCBP	Corrected to reflect total duration of required contraceptive use
Section 6.2: Exclusion Criteria and Synopsis	Added specifics regarding petechiae on brain imaging	To ensure participant safety, the definition of petechiae was clarify to include only hemorrhagic infarction type 1 (HI1) defined petechiae on brain imaging
	Added "other PPIs" to acceptable concomitant medications and disallowed cimetidine as an H2 blocker	To allow for regional differences in PPI use and to minimize any impact on the PK of clopidogrel by disallowing cimetidine as it inhibits CYP2C19
	Added reference to appendices including strong CYP3A inhibitors and inducers	To support sites in the quick identification of strong CYP3A4 inhibitors and inducers.
Section 7.1: Treatments Administered Table 7.1-1	Revised description of Investigational Products (IPs) in table	To avoid confusion and allow flexibility for future revisions to supplied IP.
	Changed the clopidogrel loading dose from 300 mg to 300 mg to 600 mg when administered as standard-of-care prior to the signing of informed consent	To allow for regional or institutional practices for clopidogrel loading dose.
Section 7.3: Selection and	Added dosing instructions for missed doses	To provide detailed guidance for the handling of missed doses of blinded study medication

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Timing of Dose for Each Participant		
Section 7.4: Blinding	Added scenarios where the DMC and the RAR vendor will receive unblinded data for safety assessment	Updated for consistency with DMC role and study design
Section 7.7.1: Prohibited and/or Restricted Treatments	Shortened the time for collection of medications taken prior to study drug administration from 30 days to 7 days Added reference to appendices including strong CYP3A inhibitors and inducers	Revised to remove burden from sites and participants To support sites in the quick identification of strong CYP3A4 inhibitors and inducers
Section 8.1: Bleeding	Removed measures that may be considered for management of bleeding events and referred to Section 9.2.1	To update the guidance for the handling of bleeding based on newly available information
Section 8.4: Emergency Procedures	Added guidance for use of thrombolytic therapy for the treatment of new stroke, including possibility of unblinding	Based on Investigator feedback, added further guidance on the handling of the blinded study medication if a subject qualifies for tPA treatment after a new stroke event.
Section 8.7: Post-Study Treatment Follow-up	Clarified required assessment for subjects who have study drug discontinued	To provide further guidance to sites regarding required study related activities in the case of early treatment discontinuation.
Section 9.2.1: Bleeding	Added measures to consider for management of bleeding events requiring intervention	To update the guidance for the handling of bleeding events that require intervention based on newly available information.
Section 9.2.3: Time Period and Frequency for Collecting AE and SAE Information	Modified required duration of SAE collection from 30 days to 7 days	Modified to coincide with BMS-986177 half-life

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.2.7: Pregnancy	Updated language for scenario where study treatment may be re-initiated following pregnancy	Update to align with BMS protocol model document
Section 9.2.8: Overdose	Updated definition of overdose to match Appendix 3	To align the definition of overdose throughout the protocol
Section 9.2.13	Added details for brief physical exam	To clarify assessments that constitute protocol-required brief physical exam
Section 9.2.16: Clinical Safety Laboratory Assessments	Clarified collection schedule for clinical laboratory samples; added Day 60 sample	Day 60 central clinical laboratory assessment added [redacted].
Section 9.3.1: PK Assessments and Section 9.3.2.1: Biomarker Sampling Schedule	Changed the collection window for the 12-hour post first dose PK/PD sample on Day 1 from ±4 hours to - 6/+4 hours. Clarified the expectation for the protocol-specified 12- and 24-hour sample collection for participants with TIA and explained that the blood sample should be collected prior to hospital discharge if the participant is released <24 hours after the index event.	Broadened the sampling window from + 4 hours to -6/+4 hours to ensure that the 12-hour post dose sample does not overlap with the 2nd dose of blinded study medication To allow for regional or institutional practice variation regarding hospitalization durations of TIA patients
Section 9.4.2: Assessment of Risk for Subsequent Stroke Associated with Index TIA	Modified text to reflect that the presence of motor symptoms can also be used as one of the qualifying criteria for TIA	To allow for enrollment of TIA patients with an $ABCD^2$ score of ≥6 in the presence of motor symptoms
Section 10.1: Sample Size Determination and Synopsis	Clarified the composite event rate that is being used for sample size determination Revised assumption for sample size determination for subjects who discontinue early without usable endpoint data from 5% to 10%	Added for clarity of composite event rate being used to determine sample size Revised to align with RAR report

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.4.2: Efficacy Analyses	Modified section to tabular form matching endpoints and statistical method	To align with preferred presentation of endpoints and methods
Section 10.4.3: Safety Analyses	Modified section to tabular form matching endpoints and statistical method Added new exploratory objective endpoint	To align with preferred presentation of endpoints and methods
Section 10.4.7: Interim RAR Analyses	Added scenarios where interim RAR will be used to stop the trial early for futility or expected success	To clearly define early stopping criteria for the study based on the event rate of clinical stroke and covert brain infarction
Appendix 4	Revised total duration of contraceptive use for WOCBP from 32 days to 34 days	Corrected inconsistency for total duration of required contraceptive use
Appendix 11	Added new appendix for strong CYP3A inhibitors	Added to inform sites of commonly administered medications that may qualify
Appendix 12	Added new appendix for strong CYP3A inducers	Added to inform sites of commonly administered medications that may qualify

Overall Rationale for Revised Protocol 02, 31-Oct-2018

[redacted] Key changes include the addition of a Day 60 central clinical laboratory sample and review by the DMC after the first 450 subjects complete the Day 21 visit. The PK sampling schedule was changed for Days 21 and 90; PD sample collection changed to be consistent with the revised PK sample times and sample collection window. The BMS-supplied aspirin and clopidogrel designation was changed from non-Investigational Product (Non-IP) to IP. INR was added to the blinded analytes on Days 21 and 90. Additionally, Appendix 3 (Adverse Events) was updated as part of standardization of AE collection procedures and details by the Sponsor.

No objectives or endpoints have been changed from the original protocol, except for the removal of Barthel Index. Other changes are administrative changes that do not impact the scientific integrity of the study, such as typographical errors or clarifications and changes in terminology. The changes made in the body of the protocol were also implemented in the Synopsis where applicable. The table below highlights the key changes made to the body of the protocol starting at Section 2.

Summary of Key Changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2: Table 2-2	Updated table to reflect addition of central clinical laboratory sample collection at Day 60 site visit with expanded visit window. Added evaluation of MoCA and subset of WAIS-IV by central laboratory	Day 60 central clinical laboratory assessment added [redacted]. The accuracy and reliability of cognitive impairment instruments used in clinical trials is thought to be improved by central laboratory evaluation.
Section 5.1: Study Design and Synopsis	Added DMC review after the first 450 subjects to make recommendation regarding central clinical laboratory sampling. Update study schematic and approximate blood volume.	[redacted] the data from first 450 subjects who complete the Day 21 visit will be reviewed by the DMC to make a recommendation about continuing central laboratory sampling on Day 60.
Section 5.1.1: Data Monitoring and Other External Committees	Added key responsibilities of the DMC to make recommendation for continued central clinical laboratory testing.	See above for rationale. The RAR is being managed by the

Summary of Key Changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Removed details about ADC.	leading world experts for RAR design and they will be checking the model simulation results and the algorithm outputs. The probability of having an erroneous algorithm is very low. In addition, the DMC will review the RAR results every 2 months. The DMC statistician has sufficient experience to assess whether the algorithm and randomization allocation are reasonable.
Section 7.1, Table 7.1-1: Study Treatments for CV010031	Updated description of placebo for BMS-986177 treatments and changed designation of aspirin and clopidogrel from non-investigational product (IP) to IP	Because BMS is providing the aspirin and clopidogrel, the designation was updated to reflect standard process.
Section 7.2: Method of Treatment Assignment	Clarified details related to the use of the IRT system	Updated to reflect proper terminology for use of the IRT system
Section 9.2.8: Overdose	Updated overdose text to reflect new definitions in the updated Appendix 3	Updated to reflect updated Appendix 3 which describes AE collection, definition and reporting requirements
Section 9.2.16: Clinical Safety Laboratory Assessments	INR added to the blinded analytes on Days 21 and 90	Inconsistency corrected for blinding of coagulation factors
Section 9.3.1.1, Table 9.3.1.1-1	Modified PK collection times relative to dose to 2 Hours (-2/+4) for BMS-986177, aspirin and clopidogrel on Days 21 and 90	The earlier timepoint for aspirin and clopidogrel sampling will allow for more quantifiable concentrations. PK sample collection times for BMS-986177 changed to align to ease site burden for Day 21 and 90 visits
Section 9.3.2.1, Table 9.3.2.1-1	Aligned biomarker collection schedule with PK sample collection schedule by modifying Day 21 and 90 sample collection time relative to dose.	Changed to ease site burden for sample collection.

Summary of Key Changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.3.3: Additional Research Collection	Removed text indicating that end-of-study is defined as 2 years after the final study report is completed.	Modified to align with standards.
Section 9.4.4	Added evaluation of MoCA and subset of WAIS-IV by central laboratory	The accuracy and reliability of cognitive impairment instruments used in clinical trials is thought to be improved by central laboratory evaluation.
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized
Appendices	Replaced Appendix 3 to reflect updated AE reporting definitions and details.	Appendix updated as part of standardization of AE collection procedure and details by Sponsor.

Overall Rationale for Revised Protocol 01, 20-Sept-2018

The purpose of this amendment is to update the protocol in consideration of [redacted] further engagement with the Steering Committee (SC) and Key Opinion Leaders (KOLs) which provided new insights into the target population and operational feasibility of the protocol as initially written. Key changes include the scenarios for clopidogrel use prior to randomization and modification of clopidogrel loading dose from 600 mg to 300 mg. Some inclusion/exclusion criteria were modified to better define the target population. The collection of Barthel Index, to assess the impact of stoke on daily living, was removed from the protocol. The introduction of the high-dose BMS 986177 groups was modified and will now be considered in a staggered fashion after completion of up to 600 subjects and after DMC recommendation. The Day 90 MRI window was modified to reduce the probability of having missing Day 90 endpoint data due to scheduling conflict for the MRI assessment. The PK sampling schedule was revised to minimize site-level impact on Day 1 and to remove PK assessments for clopidogrel and aspirin at most study visits.

No objectives or endpoints have been changed from the original protocol, except for the removal of Barthel Index. Other changes are administrative changes that do not impact the scientific integrity of the study, such as typographical errors or clarifications and changes in terminology for "non-hemorrhagic stroke" to "ischemic stroke" and "silent" brain infarction to "covert" brain infarction. The changes made in the body of the protocol were also implemented in the Synopsis where applicable. The table below highlights the key changes made to the body of the protocol starting at Section 2.

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2: Tables 2-1 and 2-2	Updated tables to reflect change to: NIHSS score for qualifying event from ≤7 to ≤5, scenarios where a clopidogrel loading dose is needed, and revisions to the Day 90 MRI window.	Based on feedback from the SC, the clopidogrel loading dose and scenarios related to use of clopidogrel prior to randomization were reconsidered, as was the qualifying NIHSS score. Day 90 MRI window was modified to minimize the risk of lost endpoint data.
Section 4: Objectives and Endpoints Table 4-1	Updated objectives and endpoints table to reflect removal of Barthel Index and change in terminology for "non-hemorrhagic stroke" to "ischemic stroke" and "silent" brain infarction to "covert" brain infarction	Barthel Index was removed as it was thought to offer minimal additional information compared to other assessments being collected, and the collection would be outweighed by the additional operational complexity to collect multiple assessments. Terminology was modified to better align with more generally used terms.

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1: Study Design and Synopsis	Revised clopidogrel loading dose from 600 mg to 300 mg and clarified scenarios under which clopidogrel or other antiplatelet agents can be used prior to randomization. Updated study schematic (Figure 5.1-1) and clarified the Day 90 MRI window. The enrollment of participant to the 200 mg QD or BID BMS-986177 doses was also changed to be implemented in a staggered manner	Clopidogrel loading dose was reduced from 600 mg to 300 mg due to similar clinical outcomes between these two loading doses (ie, CHANCE *vs*. POINT) and concerns about site/country acceptability since the study is planned for global recruitment. The Day 90 MRI window was clarified to allow flexibility in an attempt to minimize Day 90 MRI data loss. As BMS-986177 has not been studied in this acute stroke population in combination with DAPT therapy, it is prudent for the Sponsor to take a staggered approach to ensure patient safety. Therefore, the high doses of BMS-986177 will not be started until some safety data are obtained and reviewed by the DMC.
Section 6: Study Population	Various inclusion and exclusion criteria were modified to reflect feedback from SC. Other changes were made to align with allowance for pre-randomization treatment with clopidogrel or other antiplatelet agents *vis a vis* clopidogrel loading dose scenarios. Concomitant pantoprazole use was allowed. Scenarios where UFH or LMWH were allowed for post-stroke DVT prophylaxis prior to randomization.	NIHSS score for qualifying event was changed from ≤7 to ≤5 based on feedback from SC. Additional risk factors for participants between 40-54 years of age were removed because these factors have no added value in identifying the study population but will increase site burden. Use of additional antiplatelet agents prior to randomization were allowed and details were provided where needed to limit exclusion of otherwise eligible patients. Pantoprazole use was allowed as this PPI was thought to have the least impact on clopidogrel PK and remove a barrier to enrollment for participants who need treatment with acid-reducing agents

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.2: Treatment Assignment	Section updated to reflect staggered approach for the 200-mg QD and/or BID dose groups	Randomization (previously equally allotted to 8 doses) needed to be revised to 6 doses due to the staggered approach being employed for the introduction of 200 mg BMS-986177 QD and/or BID doses.
Section 7.3: Selection and Timing of Dose for Each Participant	Timing of BMS-986177 dose to meals was removed	The dependence on meals for BMS-986177 dosing was removed as it was thought to pose additional operational difficulty with limited benefit given the anticipated small effect of food in the dose range being investigated for BMS-986177
Section 9.2.12: Magnetic Resonance Imaging (MRI)	Clarified details for Day 90 MRI window.	Expanded to Day 90 MRI window to +10 days and reinforced the need for continued treatment if participants utilize the window. MRI window intended to allow site and machine scheduling flexibility to avoid loss of data for the Day 90 MRI endpoint.
Section 9.2.16: Clinical Safety Laboratory Assessments	PT added to Clinical laboratory Assessments table for Days 21 and 90	PT added to clinical laboratory assessments as biomarker to confirm target selectivity. Results noted as "blinded to Investigator, site staff and Sponsor"
Section 9.3.1.1, Table 9.3.1.1-1	Modified PK sample collection times for BMS-986177 and removed Day 1 sampling for aspirin and clopidogrel PK. Added collection of PK samples at time of new stroke or major bleeding event	PK sample collection schedule revised to minimize site burden for sample collection during evening hours. Removed sample collection for aspirin and clopidogrel due to low benefit vs additional operational complexity. Sample collection at time of outcome event added to help characterize study drug exposure for participant having an outcome event
Section 9.3.2.1, Table 9.3.2.1-1	Aligned Biomarker collection schedule with PK sample collection schedule.	Alignment of sampling schedules to increase site compliance and pair data

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Removed CRP from biomarker assessment and added PT to sample collection schedule	collection timepoint for future PK-PD analyses. CRP removed due to low value vs operational complexity/blood volume considerations. PT added to assess target selectivity.
Section 9.4: Other Assessments	NIHSS score for qualifying event was changed from ≤7 to ≤5. Added collection of NIHSS, mRS, MoCA and DSST at the time of new stroke or major bleeding event. Removed Bathel Index from Section 9.4.4	NIHSS score for qualifying event was changed from ≤7 to ≤5 based on feedback from SC. Added/clarified which assessments are to be collected at the time of a new stroke or major bleeding event to provide information about cognitive function and stroke severity close to the time of a new outcome event. Barthel Index was removed as it was thought to offer minimal additional information compared to other assessments being collected, and the collection would be outweighed by the additional operational complexity to collect multiple assessments.
Section 10.2: Randomization	Section updated to reflect staggered approach for 200 mg QD and/or BID BMS-986177 doses	Section aligned to changes in Study Design for introduction of high-dose BMS-986177 doses.
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized
Appendices	Appendices for Barthel Index, NYHA Functional Classification, and ISTH, PLATO and BARC Bleeding Criteria removed. Other re-numbered accordingly.	Barthel Index removed from study assessments. Additional risk criteria (including NYHA Score) for participants from 40 to ≤54 years of age removed. Bleeding definitions to be provided separately in the study endpoints manual.

APPENDIX 11 COMBINED P-GP AND STRONG CYP3A INHIBITOR LIST

1) If the participant is taking or has taken one of the combined P-gp and strong CYP3A inhibitors listed below in the 7 days prior to randomization, do **NOT** randomize into the AXIOMATIC (CV010031) trial **(as per Protocol, Section 6.2, Exclusion Criteria 2f).**
2) The participant must **discontinue** the study drug **(BMS-986177)** if they require treatment with one of the strong CYP3A inhibitors listed below **(as per Section 8.5, Other Reasons for Permanent Discontinuation from Study Treatment).**
3) For questions, please submit questions to the [redacted] system at [redacted]. If the [redacted] system is unavailable at the time of your question, please call the [redacted] Medical Monitor at [redacted].

Therapeutic Class	Agent
Antibiotics	clarithromycin
	telithromycin
	troleandomycin
Antifungals	itraconazole
	ketoconazole
	posaconazole
	voriconazole
Antivirals	boceprevir
	danoprevir /ritonavir combination
	ombitasvir/paritaprevir/ritonavir combination
	ombitasvir/partiaprevir/ritonavir/dasabuvir combination
	telaprevir
Calcium Channel Blockers	mibefradil
Antidepressants	nefazodone
Cancer Treatments	idelalisib
Diuretics	conivaptan
Food Products	grapefruit juice double strength*
Kinase Inhibitors	idelalisib
Treatments of HIV	atazanavir

	cobicistat (GS-9350)
	darunavir
	elvitegravir /ritonavir combination
	indinavir
	indinavir /ritonavir combination
	lopinavir /ritonavir combination
	nelfinavir
	ritonavir
	saquinavir
	saquinavir /ritonavir combination
	tipranavir /ritonavir combination

* made from frozen concentrate and reconstituted with half the normal amount of water

Listing provided by BMS
Source: UW Drug Interaction Database, FDA Database®, Lexicomp Database® Version 0.1

[redacted]

APPENDIX 12 COMBINED P-GP AND STRONG CYP3A4 INDUCER LIST

1) If the participant is taking or has taken one of the combined P-gp and strong CYP3A inducers listed below in the 7 days prior to randomization, do **NOT** randomize into the AXIOMATIC (CV010031) trial **(as per Protocol, Section 6.2, Exclusion Criteria 2f).**
2) The participant must **discontinue** the study drug **(BMS-986177)** if they require treatment with one of the strong CYP3A4 inducers listed below **(as per Section 8.5, Other Reasons for Permanent Discontinuation from Study Treatment).**
3) For questions, please submit questions to the [redacted] system at [redacted]. If the [redacted] system is unavailable at the time of your question, please call the [redacted] Medical Monitor at [redacted].

Therapeutic Class	Agent
Antiandrogens	apalutamide
	enzalutamide
Antibiotics	rifabutin
	rifampin
Anticonvulsants	carbamazepine
	fosphenytoin
	phenobarbital
	phenytoin
	primidone
Herbal Medications	St John's Wort extract
Other Antilipemics	avasimibe
Other Antineoplastics	mitotane

Listing provided by BMS
Source: UW Drug Interaction Database, FDA database®, Lexicomp® Database Version 1.0
[redacted]