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Clinical Protocol CV006004

A Phase 2, Placebo Controlled, Randomized, Double-Blind, Parallel-Arm Study to Evaluate Efficacy and Safety of BMS-986141 For the Prevention of Recurrent Brain Infarction in Subjects receiving acetylsalicylic acid (ASA) following Acute Ischemic Stroke or Transient Ischemic Attack

Revised Protocol Number: 01
Incorporates: Amendment 06 and Administrative Letters 01 and 02

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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 01	07-Jul-2016	Incorporates Amendment 06
Amendment 06	07-Jul-2016	Changed top dose to be studied from 16 mg QD to 8 mg QD. Initiation of the 8 mg dose group will only begin following DMC review of safety and laboratory data from the Day 28 study visit for at least 10% of total planned subjects. Changes were made to some exclusion criteria to minimize subject risk. Guidance around the use of CYP3A4 inhibitors and inducers has been further clarified. The statistical sections and sample size calculations have been updated to correspond to these changes. PK sampling windows were expanded; changed requirements for contraception to be the use of one highly effective method of contraception or one less effective method of contraception; added statement to Appendix 1 that local laws and regulations may require use of alternative and/or additional contraception methods; clarified genotyping testing; provided further clarifications to assist with study implementation; updated text per new BMS protocol model document template; corrected typographical errors.
Administrative Letter 02	08-Apr-2016	Changed unit of measure on Exclusion Criteria 3c to Hemoglobin < 9 g/dL.
Administrative Letter 01	25-Feb-2016	Specified that procedures performed as part of standard of care may be used as screening data for the study. Deleted supplies to aid in keeping the study medication cold. Corrected visit numbering in the Time and Events table for Part 2.
Original Protocol	19-Nov-2015	Not applicable

SYNOPSIS

Clinical Protocol CV006004

Protocol Title: A Phase 2, Placebo Controlled, Randomized, Double-Blind, Parallel-Arm Study to Evaluate Efficacy and Safety of BMS-986141 For the Prevention of Recurrent Brain Infarction in Subjects receiving acetylsalicylic acid (ASA) following Acute Ischemic Stroke or Transient Ischemic Attack

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Each subject will be administered BMS-986141 or matching placebo once daily (QD) in a blinded fashion with open label acetylsalicylic acid (ASA) at a dose of 75 to 162 mg/day in the following treatment groups. ASA is a non-investigational product in this study.

Treatment A: Subjects will receive matching placebo (to BMS-986141) QD for up to 28 days in Part 1 of the Study or up to 90 days in Part 2 of the Study

Treatment B: Subjects will receive BMS-986141 0.8 mg QD for up to 28 days in Part 1 of the Study or up to 90 days in Part 2 of the Study

Treatment C: Subjects will receive BMS-986141 4.8 mg QD for up to 28 days in Part 1 of the Study or up to 90 days in Part 2 of the Study

Treatment D: Subjects will receive BMS-986141 8 mg QD for up to 28 days in Part 1 of the Study or up to 90 days in Part 2 of the Study

Study Phase: 2

Research Hypothesis: BMS-986141 is effective in reducing the recurrence of stroke in subjects with recent transient ischemic attack (TIA) or stroke.

Objectives:

Primary Objective:

To determine the dose-response relationship of BMS-986141 on the recurrence of brain infarction at 28 days as assessed by a composite of symptomatic ischemic stroke and unrecognized brain infarction as assessed by MRI in subjects with ischemic stroke or TIA treated with ASA.

Secondary Efficacy Objectives:

- To assess the effect of BMS-986141 on the occurrence of major adverse cardiovascular events (MACE, including all stroke, myocardial infarction, and CV death) by Day 90
- To assess the effect of BMS-986141 on the occurrence of the composite of ischemic stroke, myocardial infarction, and CV death by Day 90
- To assess the effect of BMS-986141 on incidence of symptomatic recurrent stroke up to 28 days of treatment
- To assess the effect of BMS-986141 on the occurrence of the composite of unrecognized brain infarction assessed by MRI at Day 28 and MACE by Day 90

Safety Objectives:

- To assess the effect of BMS-986141 on the composite of Major and Clinically Relevant Non-Major (CRNM) Bleeding
- To assess the effect of BMS-986141 on all reported bleeding
- To evaluate safety and tolerability of BMS-986141

Study Design: This is a randomized, double-blind, placebo-controlled, parallel-arm, study to evaluate the efficacy and safety of BMS-986141 in addition to ASA in subjects following acute ischemic stroke or transient ischemic

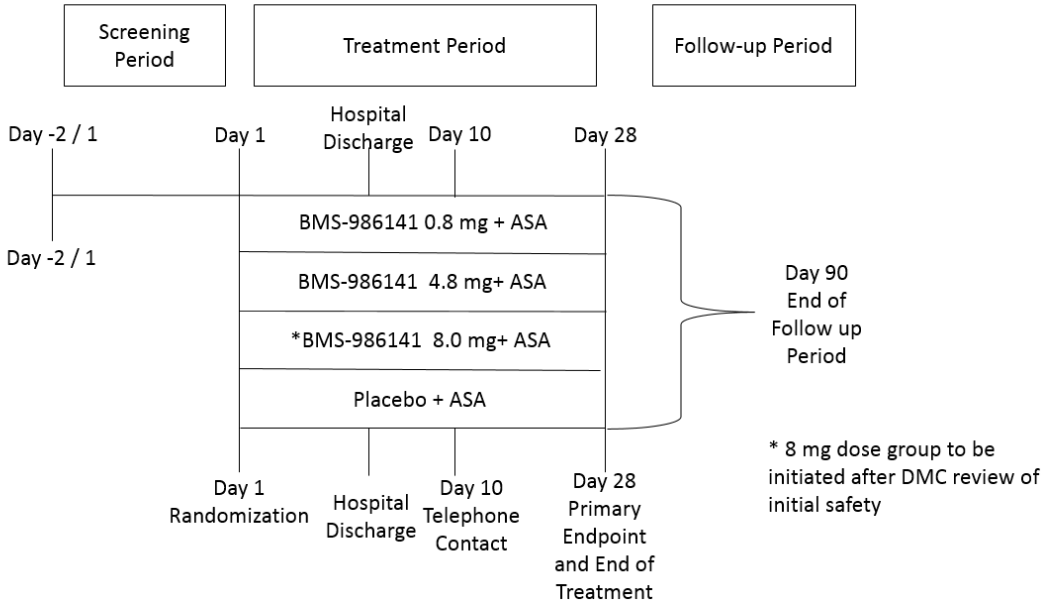
attack (TIA). Eligible subjects will be randomized within 48 hours of the time they were last seen normal prior to acute ischemic stroke/TIA and must have a baseline study-specific MRI no later than 24 hours after randomization.

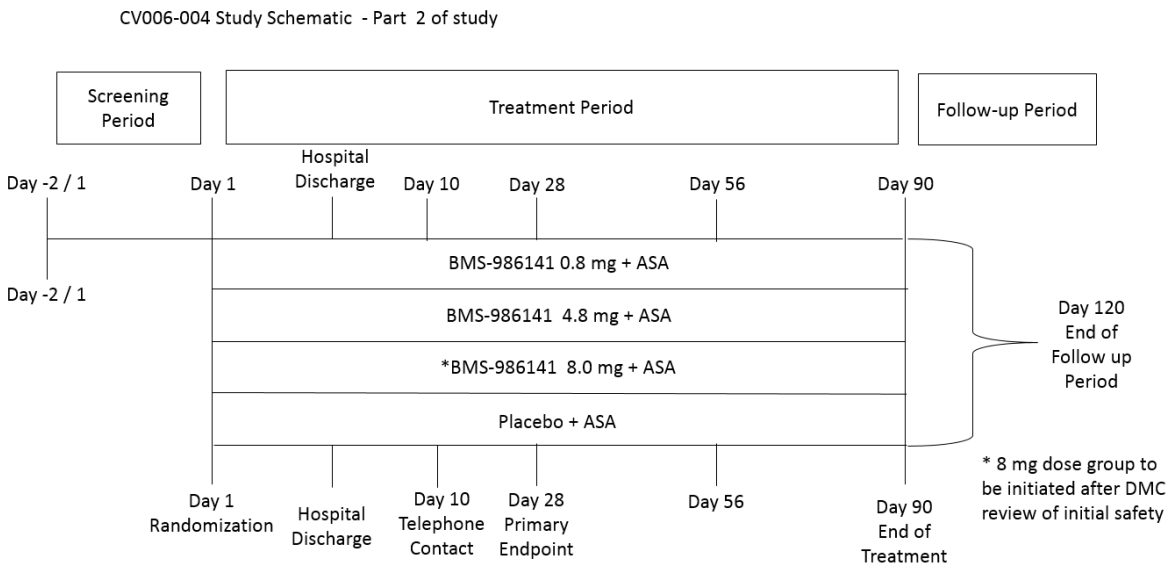
The study will be conducted in two parts. Subjects in both parts of the study will be randomly assigned to one of three different doses of BMS-986141 or matching placebo and will continue on the assigned dose for the duration of the treatment period. Initially randomization will be limited to the two lower doses of BMS-986141 or placebo. Randomization to the highest dose of BMS-986141 will only be initiated after DMC review of safety and laboratory data from the Day 28 study visit for at least 10% of the planned total subjects. In Part 1 of the study, the treatment period will be 28 days. Part 2 of the study will only be initiated after regulatory review of reports from 90-day nonclinical toxicology studies. The treatment period in Part 2 will be 90 days.

The Primary efficacy endpoint will be assessed at 28 days after the initial dose in all subjects. Additional objectives will be assessed at 28 or 90 days.

Study Schematic:

CV006-004 Study Schematic - Part 1 of study





Study Population: Male and female subjects, ≥ 18 years of age who meet the inclusion and exclusion criteria for the study as determined by medical history, physical examination, 12-lead electrocardiogram (ECG), and clinical laboratory evaluations will be eligible to participate in the study.

Potentially eligible subjects:

- Must have had an acute ischemic stroke (National Institutes of Health Stroke Scale (NIHSS) ≤ 7) or high risk TIA (ABCD2 score ≥ 4 or motor or speech symptoms; or atherosclerotic stenosis that could account for clinical presentation for which there is not a plan for revascularization therapy)
- Must have had head Computed Tomography (CT) or MRI ruling out hemorrhage or other pathology
- Randomization occurring within 48 hours after onset of symptoms; if symptoms are first present on awakening, onset should be considered as time last seen normal
- Must not have clinical evidence or any history of atrial fibrillation (other than transient AF related to cardiac surgery), severe left ventricular systolic dysfunction, left ventricular thrombus, or other high-risk cardioembolic source deemed the likely cause of brain ischemia
- Must be able to have a study-specific MRI no later than 24 hours after randomization

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

Study Drug for BMS-986141		
Medication	**Potency**	**IP/Non-IP**
BMS-986141	0.8 mg	IP
BMS-986141	4 mg	IP
Placebo (matching to BMS-986141)	0 mg	IP
Acetylsalicylic acid	75–162 mg	Non-IP

Study Assessments:

Safety: The main safety outcome of the study is bleeding. Subjects with bleeding or suspected bleeding will undergo confirmatory laboratory or other testing (ultrasound [US], CT, MRI, etc.) and an (S)AE CRF must be completed. All

clinically overt bleeding events that lead to medical treatment or evaluation, or discontinuation of study medication must be submitted for adjudication. Bleeding will be adjudicated by a blinded Clinical Events Adjudication Committee (CEC) according to definitions adapted from the International Society on Thrombosis and Hemostasis (ISTH). Bleeding will be classified as Major Bleeding, Clinically Relevant Non-Major (CRNM) Bleeding, or Minor Bleeding.

An independent Data Monitoring Committee (DMC), separate from the CEC, will monitor the safety of all subjects during the study and give recommendations to the Study Executive Committee. At the beginning of the study, subjects will be randomized to placebo, 0.8 or 4.8 mg of BMS-986141, with no subjects being randomized to the 8 mg dose. The DMC will review safety data when at least 10% of the total planned subjects for the study have completed their scheduled Day 28 visit and clinical laboratory results and other safety data from those subjects are available. Data to be included in that review will be specified in the DMC charter. As a result of this review, the DMC can recommend expansion of the randomization to all 4 study arms, additional experience on placebo and the 2 lower doses, or other modifications as necessary to ensure subject safety.

Efficacy: The primary efficacy endpoint of the study is the incidence of a composite of symptomatic ischemic stroke by Day 28 and unrecognized brain infarction assessed by MRI at Day 28. Additional Secondary Efficacy Endpoints include Major Adverse Cardiovascular Events, including symptomatic stroke, myocardial infarction, and cardiovascular death. Symptomatic efficacy events will be adjudicated by the CEC. Unrecognized brain infarction will be adjudicated by a blinded imaging adjudication committee (IAC) based on comparisons of MRI at baseline and Day 28.

Statistical Considerations:

Sample Size:

The primary efficacy endpoint of the study is the incidence of a composite of symptomatic ischemic stroke by Day 28 and unrecognized brain infarction at Day 28. Initially, randomization will be limited to the two lower doses of BMS-986141 (0.8 mg or 4.8 mg) or placebo in a 1:1:1 ratio until after DMC review of safety and laboratory data from the Day 28 study visit for at least 10% of planned total subjects (approximately 132 subjects). If the DMC recommends proceeding to inclusion of the highest dose (8 mg), subsequent randomization will be in a 1:1:1:1 ratio. Based on the staggered randomization and with a total of 1240 evaluable subjects, there is at least 80% power to demonstrate a dose-response relationship assessed by MCP-Mod method (see below), with Emax and logistic models included as candidate models, and using a 1-sided type I error of 15%. This assumes a true incidence for placebo of 14%, a maximum relative risk reduction of 30% for BMS 986141 8mg compared to placebo, and reductions of 75% and 90% of the maximum reduction for the 0.8 and 4.8 mg doses, respectively. To account for about 5% of subjects without post-randomization data, a total of 1312 subjects will be randomized.

Endpoints:

Primary efficacy endpoint

The primary efficacy endpoint of the study is the incidence of a composite of symptomatic ischemic stroke by Day 28 and unrecognized brain infarction assessed by MRI at Day 28.

Additional efficacy endpoints

Secondary endpoints:

- The incidence of major adverse cardiovascular events (MACE) by Day 90, defined as a composite of all adjudicated stroke, myocardial infarction, or CV death
- The incidence of the composite of adjudicated ischemic stroke, myocardial infarction, and CV death by Day 90
- The incidence of adjudicated symptomatic stroke (including fatal and non-fatal) by Day 28
- The incidence of the composite of unrecognized brain infarction assessed by MRI at Day 28 and MACE by Day 90

Primary safety endpoint

The primary safety endpoint will be incidence of a composite of adjudicated major bleeding and adjudicated CRNM bleeding during the treatment period.

Additional safety endpoints

- Additional safety endpoints include the incidence of adjudicated major bleeding events, all bleeding events, intracranial hemorrhage events, as well as the incidence of AEs and markedly abnormal standard clinical laboratory test results.

Analyses:

Adjudicated results will be the basis for the primary and secondary analyses.

Primary Efficacy Endpoint Analysis:

- To demonstrate the dose-response relationship between BMS-986141 treatment (including placebo) and primary endpoint, the primary analysis will be based on an MCP-Mod analysis. This analysis tests for a dose-response relationship, allowing for uncertainty in the dose-response relationship through inclusion of contrasts from pre-specified candidate models to assess dose-response. Fitted estimates for the incidence of the primary endpoint will be calculated in each of the treatment groups using a weighted model-averaging method
- The incidence of the composite of adjudicated symptomatic recurrent ischemic stroke by Day 28 and unrecognized brain infarction at Day 28 will also be summarized by treatment. Point estimates and 95% CIs for event rates will be presented by treatment, together with point estimates and 95% CIs for the relative risk reduction between each BMS-986141 arm and placebo
- A single categorical variable based on study change points (length of treatment [28 or 90 days] and randomization phase [randomized prior to or after DMC safety interim analysis decision]) will be included as a covariate

Secondary Efficacy Endpoint Analyses

- Similar analysis methods will be used for the secondary endpoint incidence of MACE as for the primary endpoint
- A sequential testing approach will be used for the primary and MACE endpoints. Dose-response relationship for the primary endpoint will be tested first using a one-sided 0.15 type I error; if the p-value for this comparison is < 0.15, then the dose-response relationship for the same endpoint will be tested using a one-sided 0.025 type I error. If the p-value for this comparison is < 0.025, then the dose-response relationship for the MACE endpoint will be tested using a one-sided 0.025 type I error
- Other secondary endpoints will use similar analysis methods as the primary and secondary endpoint of MACE

Safety analysis:

- For safety analyses, separate summaries taking into account length of treatment (28 or 90 days) and randomization phase (randomized prior to or after DMC safety interim analysis decision) will be provided
- The incidences of the composite of major bleeding and clinically relevant non-major (CRNM) bleeding, all bleeding events (including major bleeding, clinically relevant non-major bleeding and minor bleeding), and intracranial hemorrhage during the treatment period will be summarized by treatment. Point estimates and 95% CIs for event rates of each of above safety endpoint will be presented by treatment, together with point estimates and 95% CIs for the difference of event rates between each BMS-986141 arm and placebo. A single categorical variable based on study change points (length of treatment [28 or 90 days] and randomization phase [randomized prior to or after DMC safety interim analysis decision]) will be included as a stratum in the calculation of the CIs
- All other safety endpoints will be summarized descriptively by treatment

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[redacted]

1.2 Research Hypothesis

BMS-986141 is effective in reducing the recurrence of stroke in subjects with recent TIA or stroke.

1.3 Objectives(s)

1.3.1 Primary Objectives

To determine the dose-response relationship of BMS-986141 on the recurrence of brain infarction at 28 days as assessed by a composite of symptomatic ischemic stroke and unrecognized brain infarction as assessed by MRI in subjects with ischemic stroke or TIA treated with ASA.

1.3.2 Secondary Objectives

- To assess the effect of BMS-986141 on the occurrence of major adverse cardiovascular events (MACE, including all stroke, myocardial infarction, and CV death) by Day 90
- To assess the effect of BMS-986141 on the occurrence of the composite of ischemic stroke, myocardial infarction, and CV death by Day 90
- To assess the effect of BMS-986141 on incidence of symptomatic recurrent ischemic stroke up to 28 days of treatment
- To assess the effect of BMS-986141 on the occurrence of the composite of unrecognized brain infarction assessed by MRI at Day 28 and MACE by Day 90

1.3.3 Safety Objectives

- To assess the effect of BMS-986141 on the composite of Major and Clinically Relevant Non-Major (CRNM) Bleeding
- To assess the effect of BMS-986141 on all reported bleeding
- To evaluate safety and tolerability of BMS-986141

1.3.4 Exploratory objectives

- [redacted]

1.4 Product Development Background

The Investigator Brochure (IB) for BMS-986141 provides detailed information on the preclinical pharmacology, toxicology, metabolism, pharmacokinetics, and potential for drug-drug interactions of BMS-986141.The clinical experience to date is summarized below, and additional detail can be found in the IB.

1.4.1 Clinical Pharmacology and Safety

Preliminary data have been reviewed on a total of 116 subjects who have received single doses of BMS-986141 of up to 150 mg and multiple doses of up to 30 mg QD for up to 14 days in study CV006003. This includes subjects receiving multiple doses of 20 mg QD or placebo co-administered with ASA 325 mg QD for up to 14 days and subjects who received single doses of BMS-986141 in the presence of itraconazole, a strong cytochrome P450 (CYP) 3A4 inhibitor. Preliminary results show dose proportional PK and a consistent concentration-dependent PD effect. In addition, exposures in subjects who also received itraconazole increased up to 8-fold and the half-life of BMS-986141 increased ~3-fold.

Review of preliminary safety data showed no clinically significant AEs or laboratory abnormalities, including coagulation profiles, template bleeding times, BUN, creatinine, bilirubin, or hepatic enzymes. This includes all subjects who received BMS-986141 co-administered with ASA and BMS-986141 co-administered with itraconazole.

1.4.1.1 Pharmacokinetics of BMS-986141

BMS-986141 was rapidly absorbed following oral administration to fasted healthy subjects, with maximum concentrations achieved between 1.75-3 hours. The mean terminal half-life of BMS-986141 was between 35.2-45.5 hours. The accumulation index was < 2 (ranging from 1.3 to 1.9). Both maximum concentration (Cmax) and total drug exposures of BMS-986141 increased in a dose-proportional manner.

There are 3 major circulating metabolites of BMS-986141; BMT-162856 (700 – fold less active), BMT-181551, and BMT-162853. Exposures of BMT-162856 were 6.8-36.4-fold higher than BMS-986141, with the exposures of the other metabolites much lower than BMS-986141. The exposures of BMS-986141 and its major circulating metabolites are expected to be below no-observed-adverse-effect level (NOAEL) exposures at all doses. All metabolites are expected to have minimal contribution to the overall PD effect.

1.4.1.2 Dose Selection

A combination of preclinical efficacy and safety data, inhibition of human ex vivo platelet aggregation, and Phase 1 PK, PD and safety have been taken into consideration in selecting doses for this study. Doses have been selected to optimize the ability to address the primary objective, which is to determine the dose-response relationship of BMS-986141 on the recurrence of brain infarction at 28 days as assessed by a composite of symptomatic ischemic stroke by Day 28 and unrecognized brain infarction as assessed by MRI.

1.5 Overall Risk/Benefit Assessment

The current study is a Phase 2 study of BMS-986141 in patients with ischemic stroke or TIA who are also receiving ASA. Prior to this study BMS-986141 has only been dosed in healthy subjects.

Preclinical studies in non-human primates suggest that BMS 986141 may be more effective at preventing the growth of an arterial thrombus than treatment with ASA alone. Furthermore, substantial antithrombotic efficacy has been observed at doses which increase provoked bleeding to an extent that is comparable to or less than that of ASA. Thus BMS-986141 may have the potential to provide an improved benefit-risk profile compared to existing therapies for the prevention and/or treatment of atherothrombotic diseases such as stroke.

The study and dosing scheme described herein has been designed to minimize risks to study subjects and is based on the previous clinical experience in healthy subjects and preclinical toxicity studies as described in the Investigator Brochure. There were no adverse findings in 28-day preclinical toxicology studies. In 3-month studies, the major preclinical findings of note were microscopic changes in kidneys of some of the monkeys that received the highest dose of BMS-986141, 75 mg/kg/day. These changes have been characterized as moderate degeneration and regeneration of tubular epithelium, and the effect was not observed one month after cessation of dosing. Monitoring of kidney function, urinalysis, and exploratory renal biomarkers will occur throughout the treatment period to facilitate early identification of renal abnormalities in subjects in the study.

The doses selected for this study are projected to span the anticipated pharmacologically active dose range and are considered within the safety margin indicated by the preclinical toxicology and the clinical experience in healthy volunteers. Of note, co-administration of moderate inhibitors of CYP3A4 (eg, diltiazem, verapamil) have the potential of increasing exposures of BMS-986141 beyond those observed with ASA co-administration. However, it is not anticipated that exposures will exceed those observed in Phase 1 study (CV006003).

While bleeding was not observed to any significant degree either pre-clinically or in healthy volunteers, there is a potential risk of bleeding with any antithrombotic agent. There will therefore be close monitoring of subjects for bleeding and oversight of the study by an independent Data Monitoring Committee (DMC).

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

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

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

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

2.2 Institutional Review Board/Independent Ethics Committee

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

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

2.3 Informed Consent

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

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

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

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study
- Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion
- 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 subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.

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

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

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

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a randomized, double-blind, placebo-controlled, parallel-arm, study to evaluate the efficacy and safety of BMS-986141 in addition to ASA in subjects following acute ischemic stroke or TIA. Eligible subjects will be screened for possible inclusion in the study as soon as possible after arrival at the hospital, and randomized within 48 hours of the time they were last seen normal prior to acute ischemic stroke/TIA. In order to study subjects during their period of highest risk for recurrent stroke, randomization and treatment as early as possible after admission to the hospital is preferred. A baseline study-specific MRI evaluation must be performed no later than 24 hours after randomization.

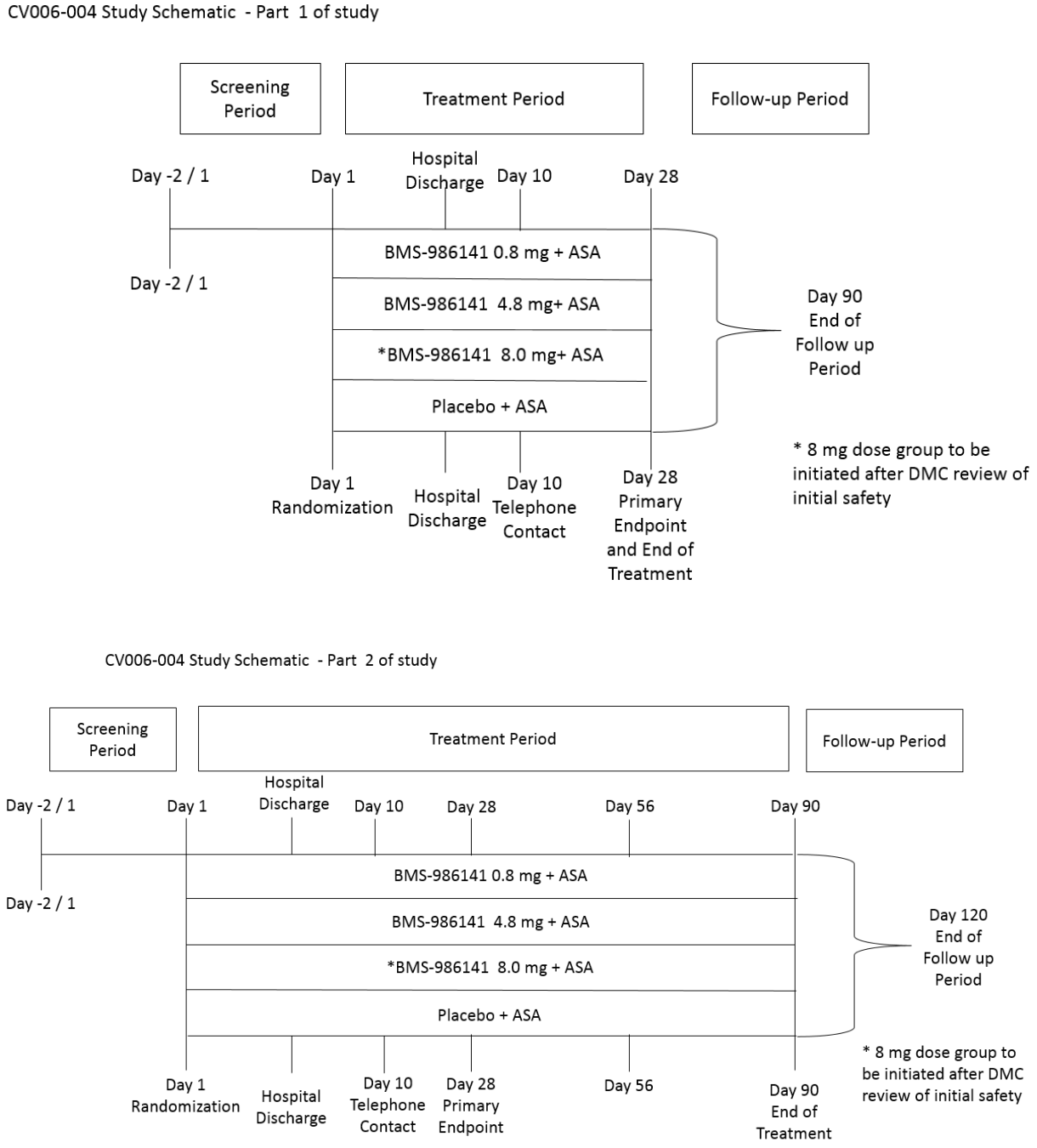
The study will be conducted in two parts. Subjects in both parts of the study will be randomly assigned to one of three different doses of BMS-986141 or matching placebo, and will continue on the assigned dose for the duration of the treatment period. Approximately 1312 subjects will be randomized into the study in total. Initially randomization will be limited to the two lower doses of BMS-986141 or placebo. Randomization to the highest dose of BMS-986141 will only be initiated after DMC review of safety and laboratory data from the Day 28 study visit for at least 10% of the planned total subjects.

In Part 1 of the study, the treatment period will be 28 days. Part 2 of the study will only be initiated after regulatory review of reports from 90-day nonclinical toxicology studies that were recently completed. The treatment period in Part 2 will be 90 days. Subjects that are entered into Part 1 of the study will not be allowed to enter into Part 2.

The primary efficacy endpoint will be assessed at 28 days after the initial dose in all subjects. Additional objectives will be assessed at 28 or 90 days.

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic



Screening Period

Subjects with acute ischemic stroke or TIA will be evaluated for study eligibility. Subjects should be evaluated and treated according to the local standard of care. Subjects who meet the inclusion/exclusion criteria are eligible. In order to prevent overrepresentation of lacunar infarction in the study population, subjects with lacunar infarction will not be able to be

randomized after a limit of approximately 20% of the total study population have been randomized with lacunar infarction. This limit will be imposed by the study IVRS. Informed consent must be obtained before any study-specific procedures are performed. Local laboratory values will be used for assessment of eligibility. A head MRI that meets criteria established for the study will be required in all subjects within 24 hours of randomization. It is preferred that imaging be performed as early as possible after enrollment. Imaging may be performed before randomization but should not be a cause of delayed randomization. Images obtained prior to screening will only be acceptable if performed under the same criteria that will be established for the Day 28 MRI. Similarly, any other study related procedures including but not limited to physical examination (PE), vital signs, or laboratory work performed as part of standard of care may be used as screening data if they meet the requirements of the study protocol.

Randomization (Day 1)

Subjects must be randomized within 48 hours of onset of symptoms of stroke or TIA. If symptoms are present on awakening, the time for onset of symptoms should be considered as the time at which they were last seen normal. Subjects will be randomized via IVRS to one of three doses of BMS-986141 or placebo. All subjects will receive open-label ASA at a dose from 75 to 162 mg per day beginning at a time consistent with local standard of care for patients with acute ischemic stroke or TIA.

Treatment Period

Subjects should receive the first dose of study medication as soon as possible after randomization and continue with once daily dosing for the duration of the treatment period. Dosing after Day 1 should be in the morning, and must be done while fasting. Subjects who receive their first dose of study medication in the afternoon or evening should be given their second dose on the morning of the second day. Subjects should be made aware of the signs or symptoms of recurrent stroke, and instructed to report any adverse events.

A study visit will be performed on the day of hospital discharge. Subjects will be instructed to report any adverse events occurring after hospital discharge, including any occurrence of bleeding or signs or symptoms of recurrent stroke.

The study site will contact the subject by telephone on Day 10 ± 3 days to assess study medication compliance and assess the subject's health status.

A study visit will be performed 28 ± 3 days after the first dose of study medication. Head MRI will be performed for assessment of unrecognized brain infarctions. For subjects enrolled in Part 1 of the study, Day 28 will be the end of the treatment period and it is preferred that the study visit be performed on Day 28 or earlier.

Part 2 of the study will only be initiated after regulatory review of 90-day preclinical toxicology study reports and the updated Investigator Brochure. For subjects enrolled in Part 2 of the study, the treatment period will be 90 days. There will be no change in study visits through Day 28. Additional treatment period study visits for these subjects will occur 56 and 90 days after the beginning of the treatment period.

Pharmacokinetic (PK) sampling will be performed in all subjects. See Section 5.5.

A sub-study conducted at select sites will enroll approximately 50 subjects per arm for which additional blood will be collected for analysis of platelet aggregation as a pharmacodynamic biomarker. See Section 5.6.

Follow-Up Period

The follow-up period will last until the later of 90 days after the first dose of study drug or 30 days after treatment discontinuation. Subjects will be instructed to report any adverse events that occur during the follow-up period. No additional study assessments are planned at the follow-up visit, which may be an in-person study visit or if necessary conducted by telephone.

Duration of Study

The expected duration of the study, from first subject, first visit through the last subject, last follow-up visit (eg, the End of the study), is approximately 28 months.

3.2 Post Study Access to Therapy

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

Treatment codes will be provided to the investigators following the final database lock and after unblinding by BMS.

3.3 Study Population

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

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Subjects or Legally Acceptable Representatives (LAR), must be willing and able to give signed and dated written informed consent. (Note: Consent by a LAR will only be allowed if permitted by local regulations.)

2. Target Population

a) Either acute ischemic stroke or high-risk TIA as defined here

i) Acute ischemic stroke, defined as:

(1) Neurological deficit attributed to the focal brain ischemia, and either of the following:

- Persistent signs or symptoms of the ischemic event at the time of randomization
- Acute, ischemic brain lesion documented by computed tomography (CT) scan or MRI

AND

(2) National Institutes of Health Stroke Score (NIHSS) ≤ 7

ii) High-risk TIA, defined as:

(1) Neurological deficit of acute onset attributed to focal ischemia of the brain by history or examination with complete resolution of the deficit, and at least one of the following:

- ABCD2 score ≥ 4 OR motor or speech symptoms
- Symptomatic intracranial arterial occlusive disease documented by transcranial Doppler, ultrasound or vascular imaging, defined as at least 50% narrowing in diameter of a vessel that could account for the clinical presentation
- Documented internal carotid arterial occlusive disease, defined as at least 50% narrowing in diameter of a vessel that is presumed to be atherosclerotic and could account for the clinical presentation
- Documented stenosis in the vertebral circulation that is presumed to be atherosclerotic and could account for the clinical presentation

b) CT or MRI ruling out hemorrhage or other pathology, such as vascular malformation, tumor, or abscess that could explain symptoms or contraindicate therapy

c) Randomization occurring within 48 hours after onset of symptoms; if the time of onset of symptoms is unknown, such as when symptoms are first present on awakening, onset should be considered as time last seen normal

d) Subject is able to be evaluated by study-specific MRI no later than 24 hours after randomization, does not have contraindications to the performance of the MRI, and has suitable weight and circumference. See Section 3.4.3 for further details.

e) Ability to tolerate ASA at a dose from 75 to 162 mg/day

f) Subject Re-enrollment: This study does not permit the re-enrollment of a subject that has discontinued the study as a pre-treatment failure

3. Age and Reproductive Status

a) Males and females, minimum age ≥ 18 years old or age of majority (if local age of majority is > 18 years of age) at the time of the screening visit

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

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) BMS-986141 plus 5 half-lives of study drug BMS-986141 (6 days) plus 30 days (duration of ovulatory cycle) for a total of 36 days post-treatment completion

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) BMS-986141 plus 5 half-lives of the study drug (6 days) plus 90 days (duration of sperm turnover) for a total of 96 days post-treatment completion. In addition, male subjects must be willing to refrain from sperm donation during this time.

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

g) Women of child-bearing potential who use hormonal contraception must agree to use an additional method of birth control (highly effective or less effective) as detailed in Appendix 1. Female partners of male subjects participating in the study may use hormone based contraceptives as an acceptable method of contraception since they will not be receiving study drug.

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

At a minimum, subjects must agree to use one highly effective method of contraception OR one less effective method as detailed in Appendix 1.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Any history of atrial fibrillation (AF) other than transient AF related to cardiac surgery

b) Severe left ventricular systolic dysfunction, left ventricular thrombus, or other high-risk cardioembolic source deemed the likely cause of brain ischemia

c) TIA symptoms limited to isolated numbness, isolated visual changes, or isolated dizziness/vertigo

d) Carotid or vertebral stenosis for which there is a plan for revascularization therapy

e) Any condition requiring ongoing treatment with an anticoagulant after discharge. For prophylactic measures to prevent deep vein thrombosis (DVT), pneumatic pressure devices are preferred

2. Medical History and Concurrent Diseases

a) Subjects with known bleeding diathesis or coagulation disorder (eg, thrombotic thrombocytopenic purpura)

b) History of previous non-traumatic or traumatic intracranial hemorrhage at any time

c) Acute gastrointestinal ulcer or history of gastrointestinal (GI) bleed which required medical treatment within the past 3 months

d) Planned or anticipated invasive surgery or procedure during study duration

e) Persistent, uncontrolled hypertension (systolic BP > 180 mm Hg, or diastolic BP > 100 mm Hg) that does not respond to acute treatment

f) Moderate or severe hepatic impairment, defined as Child-Pugh Class B or C; (see Appendix 5)

g) Moderate to severe renal impairment, defined as estimated glomerular filtration rate (eGFR) < 45 mL/min; (see Section 5.3.7.1)

h) Any other reason, in the opinion of the investigator that the subject may be at undue risk from study participation

i) Qualifying ischemic event induced by angiography or surgery

j) Any gastrointestinal surgery that could impact upon the absorption of study drug

k) Inability to tolerate oral medication or swallow tablets whole

l) Inability to undergo venipuncture and/or tolerate venous access

m) Subjects in whom MRI procedures cannot be performed. Section 3.4.3 provides a list of some common conditions that may preclude the subjects from having MRI. However, this should not be used as a substitute for local clinical standards of care. The ultimate decision to perform any of these procedures in an individual subject in this study rests with the site radiologist, the investigator and the standard set by the local ethics committee/institutional review board

n) Any other medical, psychiatric and/or social reason including drug or alcohol abuse which in the opinion of the investigator may impact the subject's ability to comply with study procedures

o) Subjects who have received intravenous or intra-arterial thrombolysis or mechanical thrombectomy within the past 48 hours or who are currently eligible and able to receive these treatments for their current stroke

3. Physical and Laboratory Test Findings

a) Any of the following on 12-lead electrocardiogram (ECG) prior to study drug administration, confirmed by repeat

i) Atrial fibrillation or atrial flutter

ii) Complete heart block or Mobitz 2 second degree heart block

iii) QRS ≥ 180 msec

iv) QT ≥ 500 msec

v) QTcF ≥ 450 msec (Not applicable per Protocol Amendment 06)

b) Platelet count < 100 x 10^3/μL (100 x 10^9/L)

c) Hemoglobin (Hb) < 9 g/dL

4. Allergies and Adverse Drug Reaction

a) History of allergy to BMS-986141, acetylsalicylic acid, or related compounds

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

c) History of drug-induced hematologic or hepatic abnormalities

5. Other Exclusion Criteria

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

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

6. Prohibited Medications

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

b) Any prior exposure to BMS-986141

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 or for prophylaxis of venous thromboembolism (VTE)

d) Planned use of antiplatelet therapy other than study medication or ASA at a dose from 75 to 162 mg. including ASA at a dose < 75 mg/day or > 162mg/day, GPIIb/IIIa inhibitors, clopidogrel, ticlopidine, prasugrel, dipyridamole, ozagrel, cilostazol, and ticagrelor. Treatment with ASA at a dose >162 mg/day before randomization is allowed.

e) Receipt of any intravenous or intra-arterial thrombolysis within 48 hours of randomization (This criterion is Not Applicable per Protocol Amendment 06; refer to Exclusion Criteria 2o)

f) Anticipated requirement for ongoing treatment with non-steroidal anti-inflammatory drugs (NSAIDs). COX-2 inhibitors are allowed. NSAID use prior to randomization is allowed

g) Use of strong CYP3A4 inhibitors or strong CYP3A4 inducers in the 7 days prior to randomization or the need for ongoing treatment with concomitant oral or intravenous therapy with strong CYP3A4 inhibitors or strong CYP3A4 inducers during the study.

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

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

Any investigational drug or placebo exposure during and 60 days post study drug administration is prohibited.

Use of the following treatments is prohibited during the treatment period:

- Anticoagulants including warfarin or other vitamin K antagonists, oral thrombin and factor Xa inhibitors, bivalirudin, hirudin, argatroban, unfractionated and LMWH, with the exception of heparin or LMWH used to maintain patency of indwelling catheters or for prophylaxis of VTE
- Antiplatelet therapy other than study medication or ASA at a dose from 75 to 162 mg/day including ASA at a dose < 75 mg/day or > 162 mg/day, GPIIb/IIIa inhibitors, clopidogrel, ticlopidine, prasugrel, dipyridamole, ozagrel, cilostazol, and ticagrelor
- Requirement for treatment with concomitant oral or intravenous therapy with strong CYP3A inhibitors or CYP3A4 inducers
- Ongoing treatment with non-steroidal anti-inflammatory drugs (NSAIDs); COX-2 inhibitors are allowed

For WOCBP the use of hormonal contraceptives should not be the primary method of contraception; women may continue on these medications but must commit to using another method of highly effective birth control while on study. See Section 3.3.1.

The following medical procedures are prohibited while the subject is receiving study medication: carotid revascularization such as endarterectomies and stenting.

If treatment with the therapies noted above, except for strong CYP3A4 inhibitors or strong CYP3A4 inducers, becomes necessary, the study medication should be stopped temporarily up to a maximum of 14 days while subjects are treated with the prohibited medications. Study medication should be restarted upon completion of treatment with the prohibited therapy. Subjects who will require treatment with strong CYP3A4 inhibitors or strong CYP3A4 inducers must be discontinued from study treatment. It is recommended the strong CYP3A4 inhibitor or inducer is not started until at least 24 hours after the last dose of study medication. For guidance related to dosing of study medication, please refer to Section 4.5.

3.4.2 Other Restrictions and Precautions

The potential for drug interactions between BMS-986141 and statins (eg, atorvastatin, rosuvastatin, simvastatin) has not been evaluated in a clinical study and may occur when they are taken at the same time. Statins should be dosed at least 4-6 hours after administration of BMS-986141.

It is strongly recommended that subjects refrain from drinking grapefruit juice throughout the duration of the treatment period of the study.

3.4.3 MRI Contraindications

1) Subjects who have a history of claustrophobia.
2) Subjects who have a physical limitation related to fitting in the bore of the magnet (ie, weight greater than that allowable by the MRI table).

3) Subjects with a pacemaker, 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) Subjects with MRI-incompatible cochlear implants.
5) Subjects with spinal nerve stimulators.
6) Subjects with an infusion pump.
7) Subjects with tattoos near the eye.
8) Subjects with metallic fragments in the eyes/orbits or in the vicinity of the brain or major neurovascular structures of the body.
9) Subjects with an employment history, which involves exposure to welding; unless absence of metallic fragments is documented by X-ray examination as per institutional practice.
10) Subjects who have shrapnel at any place in their body.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

During treatment period circumstances may arise which require temporary or permanent discontinuation of investigational product. For guidance related to the temporary discontinuation please refer to Section 3.4.1.

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

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Any clinical condition requiring treatment with a prohibited medication for more than 14 days
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Severe non-compliance to protocol, as judged by the investigator and/or Sponsor (BMS)
- Incorrect enrollment (ie, the subject does not meet the required inclusion/exclusion criteria) for the study, as determined after consultation with the sponsor
- Pregnancy
- Moderate or severe renal impairment defined as eGFR < 45 mL/min (see section 5.3.7.1) for more than 7 days.
- Subjects with an ALT and/or AST > 3× ULN will be scheduled for a follow up visit within 3 days following the receipt of the result. Subjects should be discontinued from study if the initial and repeat laboratory tests meet any of the following criteria:
    - ♦ ALT and/or AST are > 3× ULN and total bilirubin (TB) > 2× ULN

- ♦ ALT and/or AST are > 5× ULN for ≥ 14 consecutive days, at any time after initial confirmatory results
- ♦ ALT and/or AST are ≥ 10× ULN

- Subjects requiring treatment with strong CYP3A4 inhibitors or strong CYP3A4 inducers
- Subjects treated with any intravenous or intra-arterial thrombolysis or with mechanical thrombectomy

In the case of pregnancy, the investigator must immediately notify the Sponsor or designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please contact the Sponsor or designee within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the Sponsor or designee must occur.

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

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

3.6 Post Study Drug Study Follow up

In this study, major adverse cardiovascular events (MACE) and the Day 28 MRI is a key endpoint of the study. Post treatment follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

3.6.1 Withdrawal of Consent

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

3.6.2 Lost to Follow-Up

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

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

4 STUDY DRUG

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

Table 4-1: Study Drugs for CV006004: Parts 1 and 2

Product Description / Class and Dosage Form	Potency	IP / Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
BMS-986141-01 Tablet	0.8mg	IP	Blinded	Plain, white to pale-yellow, oval tablet	Store at 2-8°C; In a tightly closed container; light and moisture protected
BMS-986141-01 Tablet	4mg	IP	Blinded	Plain, white to pale-yellow, oval tablet	Store at 2-8°C; In a tightly closed container; light and moisture protected
BMS-986141-01 Tablet	Placebo for 0.8 mg and 4 mg	IP	Blinded	Plain, white to pale-yellow, oval tablet	Store at 2-8°C; In a tightly closed container; light and moisture protected
Acetylsalicylic acid (ASA)	As available locally such that dose is 75-162 mg	Non-IP	Open	Commercially Sourced (Not Provided by BMS)	Per manufacturer's instructions.

4.1 Investigational Product

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. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

4.2 Non-investigational Product

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

In this protocol, non-investigational product(s) are: Acetylsalicylic acid (ASA).

The Sponsor will not be providing the ASA. It should be sourced locally by the investigator in commercial packaging.

4.3 Storage of Study Drug

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

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

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

The blinded study medication requires refrigeration and protection from light and moisture. While at the study site the blinded study medication must be maintained at a temperature between 2-8^{o}C.

Subjects will be instructed to ensure study medication is kept refrigerated between 2-8^{o}C and protected from light and moisture while in their possession. Refer to Table 4-1 for the specific storage requirements for the blinded study medication.

4.4 Method of Assigning Subject Identification

At the screening visit each subject will be assigned a unique sequential subject number by the Interactive Voice Response System (IVRS). The subject number will consist of 5 digits which are assigned sequentially (00001, 00002, 00003, etc.) by the IVRS. This number will be used for identification throughout the study and will not be used for any other participant. Screening of subjects with lacunar infarcts will be capped at approximately 20%.

Randomization schedules will be generated by BMS and kept by the IVRS vendor. Subjects will be randomly assigned to 1 of the 4 blinded treatment groups (BMS-986141 0.8 mg, BMS-986141 4.8 mg, BMS-986141 8 mg, or placebo) by the IVRS. Randomization will be limited to the two lower doses of BMS-986141 or placebo in a 1:1:1 ratio until after DMC review of safety and laboratory data from the Day 28 study visit for at least 10% of the planned total subjects. If the DMC recommends proceeding to inclusion of the highest dose, subsequent randomization will be in a 1:1:1:1 ratio.

At all study visits when study drug is dispensed, each subject will be assigned a container number by the IVRS. 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 eCRF. The IVRS will be available 24 hours per day, 7 days a week.

4.5 Selection and Timing of Dose for Each Subject

Study drug may be administered in the clinical facility or self-administered by the subject 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 subject with their daily dosing.

Double blind study medication (BMS-986141 or matching placebo) will be taken once daily. The first dose of study medication should be taken as soon as possible after randomization. Subsequent doses including on Day 2 of the study should be taken in the morning and before breakfast. The subject must be in a fasted state for at least two (2) hours when taking study medication. Subjects should wait at least one (1) hour before consuming food.

Initially, each daily dose of double blind study medication will consist of 4 tablets. The double blind treatment period will be 28 days for Part 1 of the study and 90 days for Part 2 of the study. Drug supplies that may become available in early 2017 may allow for dosing with 2 tablets per day. Sites will be provided with instructions and guidance on how to implement this change if it is to occur.

Subjects treated in Part 1 of the study MUST be instructed to stop study medication dosing on Day 28, even if visit will not occur on exactly Day 28.

Sparse PK sampling will occur at the Day 28 visit. Subjects will be instructed not to take their study medication dosage on Day 28 prior to coming to the study site.

Additional drug, dosage and mode of administration

All subjects will be dispensed open label ASA at a dose prescribed by the investigator (not less than 75 mg and not to exceed 162 mg per day). It is recommended subjects remain on the same dose of ASA throughout the treatment period.

4.5.1 Dose Modifications

The dosage of double blind study medication may not be increased or decreased during the treatment period. Double blind study medication may be interrupted if treatment with prohibited or restricted concomitant therapies is needed. Refer to Section 3.4.1.

4.6 Blinding/Unblinding

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 subject in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the investigator. The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual subject's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the subject'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 subject 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 subject has been made.

For this study, the method of unblinding for emergency purposes is IVRS.

For further instructions on how to unblind in the event of an emergency please consult the IVRS manual provided for this study. Following the unblinding of a subject's treatment the Investigator shall notify the Medical Monitor.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind.

Any request to unblind a subject for non-emergency purposes should be discussed with the Medical Monitor.

Except as noted, BMS Research and Development personnel and all vendors responsible for the conduct of the trial (protocol team) will remain blinded for the duration of the trial. Staff of BMS Research and Development that are independent from the protocol team will be unblinded to pharmacokinetic data during the course of the trial and may make recommendations to enroll additional participants to specific dosage tiers in order to obtain sufficient exposures. Any such recommendations will be considered by the Steering Committee and DMC.

The DMC will assess safety on an ongoing basis, and will have access to unblinded treatment codes. 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. The pharmacokineticist or designate in Clinical Pharmacology and Pharmacometrics; and programmers in Data Sciences may be unblinded in order to prepare preliminary summaries of pharmacokinetic and safety data as needed before data is more generally unblinded. This unblinded analysis team will not provide any information from unblinded analyses to the protocol team until after the trial completes.

The Bioanalytical Sciences section or its designate will be unblinded to the randomized treatment assignments in order to minimize unnecessary analysis of samples from control group subjects. Likewise, the Biotransformation section or its designate may be unblinded, if

metabolite profiling work is conducted. This unblinded analysis team will not provide any information from unblinded analyses to the protocol team until after the trial completes.

Platelet aggregation will be collected and reviewed for QC purposes by hospital and vendor personnel not associated with the clinical conduct of the study. During the double-blind treatment period, platelet aggregation will be masked to the Investigator and protocol team. One biomarker representative and/or designate, may be unmasked to review the platelet aggregation data, and will not provide any information that can potentially be unblinding to the protocol team until after the trial completes. The unmasked platelet aggregation data will be provided to the study team after the study has been completed.

4.7 Treatment Compliance

Each time study medication (BMS-986141/placebo and ASA) is dispensed, compliance will be reinforced, and subjects will be given a dosing diary to complete. When study medication is returned, compliance will be assessed based upon the subject's interview, review of the diary and a count of the tablets 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 subjects should be re-educated regarding treatment compliance and/or the recording of dosing in the dosing diary.

4.8 Destruction or Return of Investigational Product

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

If...	Then...
IP supplied by BMS (including its vendors)	Any unused IP supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless IP containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If IP will be returned, the return will be arranged by the responsible Study Monitor.
IP sourced by site, not supplied by BMS (or its vendors) (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

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

- On-site disposal practices must not expose humans to risks from the drug

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

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

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

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

4.9 Retained Samples for Bioavailability / Bioequivalence

Not Applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (CV006004)

Procedure	Screening (Visit 1)	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	
NIH Stroke Scale (NIHSS)	X	For anyone presenting with acute neurological deficit
ABCD2	X	For TIAs only
Ischemic Stroke Sub-typing (Oxfordshire (OCSP) classification)	X	For strokes only
Medical History	X	
Safety Assessments		
Physical Examination	X	
Physical Measurements	X	Height, Weight
Vital Signs	X	To be done prior to blood draws and ECG.
Electrocardiogram (ECG)	X	12 lead
Concomitant Medications	X	
Assessment for Serious Adverse Events	X	All SAEs must be collected from the date of subject's written consent until 30 days post discontinuation of dosing or subject's participation in the study, if the last scheduled visit occurs at a later time.
Local Laboratory Tests		Screening laboratory tests to be analyzed at a local lab. Retesting should be done locally during screening.
Plasma aPTT, INR and PT	X	

Table 5.1-1: Screening Procedural Outline (CV006004)

Procedure	Screening (Visit 1)	Notes
Pregnancy test (serum or urine) WOCBP only	X	Pregnancy test to be done locally at screening. All WOCBP must have a negative pregnancy test within 24 hours prior to dosing.
Follicle stimulating hormone (FSH) Test	X	Post-menopausal women under age 55 only. See Appendix 1.
Clinical Chemistry	X	
Hematology	X	
Urinalysis	X	
MRI	X	At Screening or No later than 24 hours after randomization

Table 5.1-2: Part 1 Procedural Outline (CV006004)

Procedure	Day 1 (Visit 2)	Day of Hospital Discharge[a] (Visit 3)	Day 10 Telephone Contact[b] (Visit 4)	Day 28 (EOT) / Early D/C[a,b] (Visit 5)	Follow-up Day 90[a,b] (Visit 6)	Notes
Safety Assessments						
Physical Examination		X		X		
Physical Measurements		X		X		Weight
Vital Signs		X		X		To be done prior to blood draws and ECG.
Electrocardiogram (ECG)				X		12-lead
Concomitant Medications	X	X	X	X	X	
Assessment of Non-Serious Adverse Events	X	X	X	X	X	
Assessment for Serious Adverse Events	X	X	X	X	X	All SAEs must be collected from the date of subject's written consent until 30 days after discontinuation of dosing or subject's participation in the study, if the last scheduled visit occurs at a later time.
Central Laboratory						Chemistry and hematology samples for Day 1 pre-dose labs and those drawn throughout the study to be analyzed by the central laboratory. Urinalysis testing (refer to Table 5.3.7-1) will be done locally for all time points.
Pregnancy test (serum or urine) WOCBP only	X			X		To be done locally. All WOCBP must have a negative pregnancy test within 24 hours prior to dosing.
Clinical Chemistry	X	X[c]		X		
Hematology	X	X[c]		X		

Table 5.1-2: Part 1 Procedural Outline (CV006004)

Procedure	Day 1 (Visit 2)	Day of Hospital Discharge[a] (Visit 3)	Day 10 Telephone Contact[b] (Visit 4)	Day 28 (EOT) / Early D/C[a,b] (Visit 5)	Follow-up Day 90[a,b] (Visit 6)	Notes
Urinalysis	X	X		X		To be analyzed locally at all time points
MRI	X*			X**		*No later than 24 hours after randomization if not done prior to randomization ** +/- 3 days from Day 28 For subjects that stop treatment early the MRI should be done on Day 28
Pharmacokinetic (PK)						
Serial/Sparse Blood PK Sampling	X			X		On Day 1, the last PK sample is collected 24 hrs (+/- 11 hrs) after first dose of study medication and before Day 2 dose
Biomarker Assessments						
Platelet Aggregation	X			X		To be performed at select sites. Samples should be collected at the same time as the time-matched PK samples. Day 1-24 hr sample to be collected 24 hrs (+/- 11 hrs) after first dose of study medication and before Day 2 dose.
Exploratory Biomarker Assessments						
[redacted]	[redacted]			[redacted]		[redacted]
[redacted]	[redacted]			[redacted]		[redacted]

Table 5.1-2: Part 1 Procedural Outline (CV006004)

Procedure	Day 1 (Visit 2)	Day of Hospital Discharge[a] (Visit 3)	Day 10 Telephone Contact[b] (Visit 4)	Day 28 (EOT) / Early D/C[a,b] (Visit 5)	Follow-up Day 90[a,b] (Visit 6)	Notes
[redacted]	[redacted]					[redacted]
Clinical Drug Supplies						
Randomize	X					
Review study drug administration compliance (BMS- 986141 or matching placebo with ASA)		X	X	X		Subjects MUST be instructed to stop study medication dosing on Day 28, even if visit will not occur on Day 28. Telephone contact with subject to review medication compliance and assess subject's health status
Dispense Study Drug	X					

[a] Subjects should participate in all study visits even if study medication dosing has been discontinued.

[b] Visit window is +/- 3 days.

[c] Laboratory tests may be done on the day prior to discharge.

Table 5.1-3: Part 2 Procedural Outline (CV006004)

Procedure	Day 1 (Visit 2)	Day of Hospital Discharge[a] (Visit 3)	Day 10 Telephone Contact[b] (Visit 4)	Day 28[a,b] (Visit 5)	Day 56[a,b] (Visit 6)	Day 90 (EOT) / Early D/C[a,b] (Visit 7)	Follow-up Day 120[a,b] (Visit 8)	Notes
Safety Assessments								
Physical Examination		X		X				
Physical Measurements		X		X	X	X		Weight
Vital Signs		X		X	X	X		To be done prior to blood draws and ECG.
Electrocardiogram (ECG)				X		X		12-lead
Concomitant Medications	X	X	X	X	X	X	X	
Assessment of Non-Serious Adverse Events	X	X	X	X	X	X	X	
Assessment of Serious Adverse Events	X	X	X	X	X	X	X	All SAEs must be collected from the date of subject's written consent until 30 days post discontinuation of dosing or subject's participation in the study, if the last scheduled visit occurs at a later time.
Central Laboratory								Chemistry and hematology samples for Day 1 pre-dose labs and those drawn throughout the study to be analyzed by the central laboratory. Urinalysis testing (refer to Table 5.3.7-1) will be done locally for all time points.
Pregnancy test (serum or urine) WOCBP only	X			X	X	X[‡] X		To be performed locally. All WOCBP must have a negative pregnancy test within 24 hours prior to dosing.

Table 5.1-3: Part 2 Procedural Outline (CV006004)

Procedure	Day 1 (Visit 2)	Day of Hospital Discharge[a] (Visit 3)	Day 10 Telephone Contact[b] (Visit 4)	Day 28[a,b] (Visit 5)	Day 56[a,b] (Visit 6)	Day 90 (EOT) / Early D/C[a,b] (Visit 7)	Follow-up Day 120[a,b] (Visit 8)	Notes
								‡Home pregnancy test kit to be sent home with WOCBP subjects to perform pregnancy test on Day 84. Test result to be recorded in patient diary. Pregnancy test must also be performed at the Day 90 visit.
Clinical Chemistry	X	X[c]		X	X	X		
Hematology	X	X[c]		X	X	X		
Urinalysis	X	X		X	X	X		To be analyzed locally at all time points
MRI	X*			X**				*No later than 24 hours after randomization if not done prior to randomization ** +/- 3 days from Day 28 For subjects that stop treatment early the MRI should be done on Day 28
Pharmacokinetic (PK)								
Serial/Sparse Blood PK Sampling	X			X				On Day 1, the last PK sample is collected 24 hrs (+/- 11 hrs) after first dose of study medication and before Day 2 dose.

Table 5.1-3: Part 2 Procedural Outline (CV006004)

Procedure	Day 1 (Visit 2)	Day of Hospital Discharge[a] (Visit 3)	Day 10 Telephone Contact[b] (Visit 4)	Day 28[a,b] (Visit 5)	Day 56[a,b] (Visit 6)	Day 90 (EOT) / Early D/C[a,b] (Visit 7)	Follow-up Day 120[a,b] (Visit 8)	Notes
Biomarker Assessments:								
Platelet Aggregation	X			X				To be performed at select sites. Samples should be collected at the same time as the time-matched PK samples. Day 1-24 hr sample to be collected 24 hrs (+/- 11 hrs) after first dose of study medication and before Day 2 dose.
Exploratory Biomarker Assessments								
[redacted]	[redacted]			[redacted]				[redacted]
[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		[redacted]

Table 5.1-3: Part 2 Procedural Outline (CV006004)

Procedure	Day 1 (Visit 2)	Day of Hospital Discharge[a] (Visit 3)	Day 10 Telephone Contact[b] (Visit 4)	Day 28[a,b] (Visit 5)	Day 56[a,b] (Visit 6)	Day 90 (EOT) / Early D/C[a,b] (Visit 7)	Follow-up Day 120[a,b] (Visit 8)	Notes
[redacted]	[redacted]							[redacted]
Clinical Drug Supplies								
Randomize	X							
Review study drug administration compliance (BMS- 986141 or matching placebo with ASA)		X	X	X	X	X		Telephone contact with subject to review medication compliance and assess subject's health status
Dispense Study Drug	X			X	X			

[a] Subject should participate in all study visits even if study medication has been discontinued.

[b] Visit window is +/- 3 days.

[c] Laboratory tests may be done on the day prior to discharge.

5.1.1 Retesting During Screening or Lead-in Period

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

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

Laboratory parameters and/or assessments that are included in Table 5.1-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

5.2 Study Materials

BMS will supply the study sites with the following:

- Patient Dosing Diaries to be completed daily after hospital discharge to record study medication taken. Diaries should be completed by all randomized subjects and reviewed for accuracy and completeness by the study staff at each study visit (refer to Section 4.7). WOCBP to record Day 84 urine pregnancy test result in diary.
- Patient Emergency Card
- Protocol specified rating scales
- Electronic case report forms

The Imaging Core Lab will supply the following:

- Image acquisition guidelines and submission processes will be outlined in the CV006004 Imaging Manual, to be provided by the imaging core lab.

5.3 Safety Assessments

Only data for the procedures and assessments specified in the protocol should be submitted to BMS on a case report form. Additional procedures and assessments may be performed as part of the subject's standard of care; however, data for these assessments should remain in the subject's medical record and should not be provided to BMS, unless needed to support an AE, SAE report, adjudication dossier or specifically requested by the sponsor.

5.3.1 Imaging Assessment for the Study

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

Imaging is an important component of the study. All subjects will undergo standardized MRI at baseline and at the Day 28 visit. Images may be evaluated locally, but must also be submitted for

analysis by the Imaging Adjudication Committee. Results of centralized analysis will not be returned to the sites.

In addition, various types of imaging may be used for the clinical evaluation of suspected efficacy or safety endpoints. For these events, investigators should perform and analyze imaging and other assessments according to their normal clinical practice and the local standard of care, and base any treatment decisions on the local interpretation. Results of these assessments will also be submitted for adjudication by the CEC. Results of the adjudication by the CEC will not be returned to the sites.

5.3.2 Bleeding

The main safety outcome of the study is bleeding. Subjects with bleeding or suspected bleeding will undergo confirmatory laboratory or other testing (ultrasound [US], CT, MRI, etc.) and an (S)AE CRF must be completed. All clinically overt bleeding events that lead to medical treatment or evaluation, or discontinuation of study medication must be submitted for adjudication. Major and clinically relevant non-major bleeding will be adjudicated by CEC according to definitions specified in the CEC charter.

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

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

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

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

Clinically relevant non-major bleeding event is defined as a bleeding event that is:

- Acute clinically overt bleeding

- Does not satisfy additional criteria required for the bleeding event to be defined as a major bleeding event
- Requires medical treatment or evaluation, or leads to discontinuation of study medication.

Minor bleeding event is defined as any adjudicated bleeding event that does not meet the criteria for Major Bleeding or Clinically Relevant Non-Major Bleeding.

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

5.3.3 Physical Examination

- A complete physical examination should include general appearance, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdomen, lymph nodes, extremities, neurological, skin, and musculoskeletal
- The individual performing the physical examinations must be licensed by state law (or applicable local law) to perform this procedure

5.3.4 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, ECG is collected or any medication is administered.

5.3.5 Physical Measurements

Physical measurements, including height (Screening only) and weight will be measured at the Screening visit and at each study visit during the treatment period.

5.3.6 Electrocardiograms

A 12-lead ECG will be recorded at Screening and at the end of treatment period visits.

5.3.7 Laboratory Test Assessments

A local/central laboratory will perform the analyses and will provide reference ranges for these tests. All screening laboratory tests will be performed locally. Day 1 pre-dose labs and those drawn throughout the study should be analyzed by the central laboratory. Results of clinical laboratory tests performed at Screening must be available prior to dosing.

Unexpected abnormal results on urinalysis should be confirmed by retesting of a new, carefully obtained sample.

The following clinical laboratory tests will be performed:

Table 5.3.7-1: Laboratory Assessments

	Screening Performed by Local Laboratory (Outlined in Table 5.1-1)	Study Visits Performed at Central Laboratory except Urinalysis (Outlined in Table 5.1-2 and Table 5.1-3)
Hematology		
Hemoglobin	X	X
Hematocrit	X	X
Red blood cell count (RBC)	X	X
Total leukocyte count with differential	X	X
Absolute platelet count	X	X
Chemistry		
Aspartate aminotransferase (AST)	X	X
Alanine aminotransferase (ALT)	X	X
Total bilirubin	X	X
Direct bilirubin (done as reflex if total bilirubin is > 2 ULN)	If needed	If needed
Alkaline phosphatase	X	X
Bicarbonate		X
Lactate dehydrogenase (LDH)	X	X
Creatinine	X	X
Blood urea nitrogen (BUN)	X	X
Uric acid	X	X
Glucose (random; fasting or non-fasting)	X	X
Total protein	X	X
Albumin	X	X
Sodium	X	X
Potassium	X	X
Chloride	X	X
Calcium	X	X
Phosphorus	X	X

Table 5.3.7-1: Laboratory Assessments

	Screening Performed by Local Laboratory (Outlined in Table 5.1-1)	Study Visits Performed at Central Laboratory except Urinalysis (Outlined in Table 5.1-2 and Table 5.1-3)
Other		
Follicle stimulating hormone (FSH) - post-menopausal women under age 55 only (Refer to Appendix 1)	X	
Urine Pregnancy Test - WOCBP only (if positive reflex to serum)	X	X
Coagulation - Screening Only		
International normalized ratio (INR)	X	Will be done by Central Lab only if part of DILI Reflex
Activated partial thromboplastin time (aPTT)	X	
Prothrombin time (PT)	X	Will be done by Central Lab only if part of DILI Reflex
Urinalysis - Urinalysis Testing specified below is to be done locally for all time points		
Protein	X	X (done locally)
Glucose	X	X (done locally)
Blood	X	X (done locally)
Leukocyte esterase	X	X (done locally)
Specific gravity	X	X (done locally)
pH	X	X (done locally)
Microscopic Examination - A full microscopic examination	X	X (done locally)
Serology - Central Lab Only Done as part of DILI reflex		
HepA antibody		Will be done by Central Lab only if part of DILI Reflex
HepB surface antigen		Will be done by Central Lab only if part of DILI Reflex
HepC antibody		Will be done by Central Lab only if part of DILI Reflex

Results of all laboratory tests required by this protocol must be provided to BMS, either recorded on the laboratory pages of the CRF or by another mechanism as agreed upon between the

investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see Section 6.3) and evaluated as clinically indicated.

5.3.7.1 Renal Impairment

The exclusion and discontinuation criteria for severe renal impairment should be evaluated based on eGFR calculated by the local laboratory. In the event that eGFR is not reported by the local laboratory, it should be calculated by the Modification of Diet in Renal Disease (MDRD) Study Equation.

eGFR = 186*serum creatinine $mg/dL^{-1.154}$*$Age^{-0.203}$[*0.742 if female][*1.212 if African American]).[6,7]

5.3.8 Other Supplemental (Unscheduled) Visits

At any time during the trial, the investigator may at his/her discretion arrange for a subject to have an unscheduled (supplemental) assessment(s), especially in the case of AEs that require follow-up. If a subject is seen for an unscheduled assessment, the appropriate Supplemental Pages of the eCRF must be completed.

5.4 Efficacy Assessments

The primary efficacy endpoint of the study is the incidence of a composite of symptomatic ischemic stroke by Day 28 and unrecognized brain infarction assessed by MRI at Day 28. Symptomatic stroke is defined in Section 5.4.1. Unrecognized brain infarction is defined in Section 5.4.2.

Additional secondary efficacy endpoints include Major Adverse Cardiovascular Events (MACE), including symptomatic stroke, myocardial infarction, and cardiovascular death. Myocardial infarction is defined in Section 5.4.3. Classification of deaths is described in Section 5.4.4.

5.4.1 Symptomatic Stroke

All cases of suspected recurrent stroke will be adjudicated by a blinded Clinical Events Adjudication Committee (CEC). Further information regarding the CEC and its processes are detailed in the CEC Charter.

Diagnosis of stroke will require the abrupt onset of focal neurological symptoms lasting at least 24 hours or identification of an acute, new infarct by CT or MRI in subjects with symptoms lasting less than 24 hours. Evaluation and treatment of strokes will be according to the local standard of care. It is strongly recommended (but not required) that an imaging procedure such as a CT scan or MRI be performed to evaluate events of suspected stroke or TIA. Adjudicated strokes will be categorized by the CEC as definite ischemic, definite hemorrhagic, hemorrhagic transformation or type uncertain. Additional classification of stroke subtypes will be specified in the CEC charter.

Evaluation of suspected TIA events should be performed according to the local standard of care. If a TIA is considered to be a suspected stroke event by the investigator, the procedure for reporting a suspected stroke event should be followed and the event will be adjudicated.

5.4.2 Unrecognized Brain Infarction

MRI of the brain will be obtained in all subjects no later than within 24 hours of randomization and at the Day 28 visit as described in the Imaging Procedures Manual. The baseline and Day 28 MRIs for each subject will be reviewed independently by the blinded neuroradiologists of the Imaging Adjudication Committee to determine if any new areas of infarction have developed since the baseline MRI. These independent assessments will undergo adjudication according to the processes described in the Imaging Charter with a single, adjudicated determination recorded for each subject.

Details regarding MRI acquisition, including required sequences, slice thickness, and quality control are presented in the Imaging Procedures Manual.

5.4.2.1 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has now become the primary noninvasive modality for stroke imaging. Diffusion weighted imaging (DWI) is highly sensitive in identifying hyperacute and acute cerebral infarction, showing ischemia within minutes of vascular occlusion.[8] The stroke lesion appears bright on DWI scans in the acute and subacute stages, while chronic infarcts are characterized by dark signal on DWI[8]. Fluid-attenuated inversion recovery (FLAIR) MRI has had important applications in the imaging of stroke patients[9]. FLAIR depicts areas of tissue T2 prolongation while suppressing CSF signal, offering a sensitive method to detect lesions.[8] Hyperintensity of the ischemic brain in acute strokes is seen on FLAIR as early as 4 to 6 hours after infarction at a time when T1-weighted images (T1WI) and T2-weighted images (T2WI) are usually normal. After the first 24 hours, T1W1, T2W1, and FLAIR are most useful in subacute and chronic stroke. FLAIR and DWI sequences will be used to identify any new ischemic infarction lesions as compared to the baseline MRI. Details of study-required MRI parameters will be described in the study imaging manual.

5.4.3 Myocardial Infarction

All cases of suspected myocardial infarction will be adjudicated by the CEC based on evidence in the clinical dossier prepared for all reported suspected MI events.

An acute MI requires the presence of at least two out of the three following conditions:

- an appropriate clinical situation suggestive of an MI (eg, abnormal history, physical examination or new ECG changes)
- elevation of CK-MB or Troponin T or I ≥ 2 x ULN; if no CK-MB or troponin values are available, a total CK ≥ 2x ULN;
- new, significant (≥ 0.04 seconds) Q waves in ≥ 2 contiguous leads.

5.4.4 Classification of Death

Deaths will be categorized by the CEC as either cardiovascular or non-cardiovascular death. All deaths will be assumed to be cardiovascular unless a non-cardiovascular cause can be clearly provided.

1) Cardiovascular

   This category includes cardiac deaths (eg, cardiogenic shock, arrhythmia/sudden death, cardiac rupture) and other cardiovascular deaths (stroke, pulmonary embolism, ruptured aortic aneurysm or dissection).

2) Non-cardiovascular

   This category includes all deaths due to a clearly documented non-cardiovascular cause, such as respiratory failure (excluding cardiogenic pulmonary edema), hemorrhage (other than intracranial), infections/sepsis, neoplasm, and trauma (including suicide and homicide).

5.5 Pharmacokinetic Assessments

Blood will be drawn at the times indicated in Table 5.5-1 for pharmacokinetic assessments.

Table 5.5-1: Pharmacokinetic Sampling Schedule

Study Day	Time Relative to Dosing) Hour	Time (Relative to Dosing) Hour:Min	PK Blood Sample	Comments
1	Pre-dose	00:00	X	
1		01:00	X	Can be collected ± 30 minutes
1		02:30	X	Can be collected ± 30 minutes
1		08:00	X	Can be collected ± 4 hours
1	Pre-Day 2 Dose	24:00	X	Can be collected ± 11 hours, but must be collected before the next dose (on Day 2) If the first dose is late in the day and the Day 2 pre-dose sample does not fall within the 24 +/- 11 hr window, the sample should still be collected and the sampling time should be recorded
28	EOT, Pre-Dose	00:00	X	Must be collected prior to dose on Day 28
28		03:00	X	Can be collected ± 1 hour

5.5.1 Pharmacokinetic Sample Analyses

The PK plasma samples will be analyzed for BMS-986141 using a validated LC-MS/MS assay and a qualified LC-MS/MS assay for BMT-162856. Pharmacokinetic samples collected from a subject who received placebo will not be analyzed.

In addition, after the scheduled pharmacokinetic 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 laboratory procedure manual.

5.6 Biomarker Assessments

5.6.1 Exploratory Biomarker Assessments

Table 5.6.1-1: Biomarker Sampling Schedule

Study Day	Time (Event) Hour	Time (Relative To Dosing) Hour: Min	Platelet Aggregation[a]	[redacted]	[redacted]	Comments
1	Pre-dose	00:00	X	X	X	
1		01:00	X			Samples can be collected ± 30 minutes.
1		02:30	X			Samples can be collected ± 30 minutes.
1		08:00	X			Samples can be collected ± 4 hours
1	Pre-Day 2 Dose	24:00	X	X		Samples can be collected ± 11 hours, but must be collected before the next dose (on Day 2) If the first dose is late in the day and the day 2 pre-dose sample does not fall within the 24 +/- 11 hr window, the sample should still be collected and the sampling time should be recorded
28	Pre-Dose	00:00	X	X	X	Samples must be collected prior to dose on Day 28 Exploratory renal biomarkers do not have to be collected prior to dose
28		03:00	X			Samples can be collected ± 1 hour
56	Part 2 only				X	
90	EOT (part 2 only)/Early D/C				X	

[a] Platelet aggregation sampling only applies to subjects participating in the PK/PD sub-study. These samples should be collected at the same time as time-matched PK samples

[b] [redacted]

Platelet aggregation samples should be collected at the same time as time-matched PK samples.

5.6.1.1 [redacted]

[redacted]

5.7 Outcomes Research Assessments

Not Applicable.

5.8 Other Assessments

The following assessments are required to be done at Screening to confirm patient eligibility.

5.8.1 National Institutes of Health Stroke Scale (NIHSS)

The National Institutes of Health Stroke Scale (NIHSS) is a well-validated, reliable graded neurological examination that rates speech and language, cognition, visual field deficits, motor and sensory impairments, and ataxia.[10] The NIHSS has become a standard part of clinical assessments used in many stroke trials because of its utility to measure the neurologic deficits most often seen with acute stroke patients. It consists of 11 elements that reflect the wakefulness, vision, and motor, sensory, and language function of stroke patients. Possible scores range from 0-42 with higher scores indicating more severe deficits. Performing the NIHSS has been timed to take 5-8 minutes. Sites should only use the version of the rating scale provided by BMS for this study.

5.8.2 ABCD2

The ABCD2 (age, blood pressure, clinical features, duration, diabetes) score is a risk assessment tool designed to improve the prediction of short-term stroke risk after a TIA.[11] The ABCD2 score is calculated by summing up points for five independent factors, specifically age, blood pressure, clinical features of the TIA, duration of the TIA, and the presence of diabetes. Multiple studies have shown that as the ABCD2 score increases the risk of subsequent stroke also increases. Sites should only use the source document of this risk assessment tool provided by BMS for this study.

5.8.3 Oxfordshire Community Stroke Project (OCSP) Subtyping

The investigators of Oxfordshire Community Stroke Project (OCSP) described a method of subtyping cerebral infarctions into four clinically identifiable subgroups[12]. Using the OCSP approach, the clinical stroke is categorized based on presenting symptoms and signs. The authors pointed out that the subtyping is based on the clinical pattern at the time of maximum deficit from stroke onset. Their approach utilized the patient history and neurological examination but not the results of investigations such as imaging or cardiac rhythm monitoring. Cerebral infarcts

are subtyped as Lacunar Infarcts (LACI), Total Anterior Circulation Infarcts (TACI), Partial Anterior Circulation Infarcts (PACI), or Posterior Circulation Infarcts (POCI) based on clinical features. Descriptions of the clinical features of the subtypes can be found in their publication[12].

In recent years, the OSCP approach has been extended by utilizing the results of cerebral imaging for the classifications[13]. For this study, the last letter for each classification will indicate whether or not the index infarct is identified on imaging. The last character of the OCSP classification will be either I (infarction) for cases when the index infarct is identified on imaging or S (syndrome) for cases in which imaging has not shown the index infarct at time of classification. Strokes will be subtyped using the extended OSCP categories by the investigator during Screening for index strokes.

6 ADVERSE EVENTS

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

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

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

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

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

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320.

6.1 Serious Adverse Events

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

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)

- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

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

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

NOTE:

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

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

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with

protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing or subject's participation in the study, if the last scheduled visit occurs at a later time. If applicable, SAEs must be collected that relate to any later protocol specified procedure.

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.

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

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

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

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 drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to Sponsor (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

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

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

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

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

6.3 Laboratory Test Result Abnormalities

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

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

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

6.4 Pregnancy

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

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the Sponsor or designee within 24 hours of awareness of the pregnancy.

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

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee. In order for BMS 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.

6.5 Overdose

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

6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

   AND

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

   AND

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

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

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

7.1 Data Monitoring Committee

For the protection of subjects participating in the study, an independent Data Monitoring Committee (DMC) will review safety data including reports of bleeding. The full role of the DMC will be defined in the DMC charter. The committee will review partially unblinded accumulating data on a regular basis and will make recommendations regarding the continuing safety of subjects currently enrolled and yet to be enrolled in the trial. The DMC may recommend suspension of accrual into a BMS-986141 treatment group or early termination of the trial, for safety reasons. At all times during the course of the study, the DMC may request access to fully unblinded data if needed.

At the beginning of the study, subjects will be randomized to placebo, 0.8 or 4.8 mg of BMS-986141, with no subjects being randomized to the 8 mg dose. The DMC will review safety data when at least 10% of the total planned subjects for the study have completed their scheduled Day 28 visit and clinical laboratory results and other safety data from those subjects are available. Data to be included in that review will be specified in the DMC charter. As a result of this review, the DMC can recommend expansion of the randomization to all 4 study arms, additional experience on placebo and the 2 lower doses, or other modifications as necessary to ensure subject safety.

7.2 Independent Central Adjudication Committees

The clinical events adjudication committee (CEC) will be a blinded, independent group of clinicians experienced in the diagnosis of stroke and other cardiovascular diseases who are not otherwise involved with the study. The CEC will evaluate clinical events related to study endpoints, including adjudication of suspected symptomatic stroke, suspected myocardial infarction, bleeding, and death. The full role of the CEC and criteria for evaluation of clinical events will be defined in the CEC charter.

The imaging adjudication committee (IAC) will be an independent group of neuroradiologists experienced in the interpretation of brain MRI images. The IAC will evaluate blinded MRI images obtained no later than 24 hours after randomization and at the Day 28 study visit for detection of unrecognized brain infarctions. The full role of the IAC and criteria for evaluation of unrecognized brain infarction will be defined in the IAC charter.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The primary efficacy endpoint of the study is the incidence of a composite of symptomatic ischemic stroke by Day 28 and unrecognized brain infarction at Day 28. Sample size calculations were performed for detecting a dose-response effect with the MCP-MOD methodology using simulations with the DoseFinding package in R[14]. Simulations of 1000 clinical trials were performed, assuming a true incidence for placebo of 14%, a maximum relative risk reduction of 30% for BMS-986141 8 mg relative to placebo, and relative reductions of 75% and 90% of the maximum for the 0.8 and 4.8 mg doses, respectively. Candidate models included an Emax model and a logistic model.

Initially, randomization will be limited to the two lower doses of BMS-986141 (0.8 mg or 4.8 mg) or placebo in a 1:1:1 ratio until after DMC review of safety and laboratory data from the Day 28 study visit for at least 10% of planned total subjects (approximately 132 subjects). If the DMC recommends proceeding to inclusion of the highest dose (8 mg), subsequent randomization will be in a 1:1:1:1 ratio. Based on the staggered randomization as shown in Table 8.1-1 and the assumptions above, the study will have at least 80% power to demonstrate a dose-response relationship, using a 1-sided type I error rate of 15%. A total sample size of 1312 randomized subjects accounts for about 5% of subjects without post-randomization data.

Table 8.1-1: Randomization Targets[a]

	Placebo	0.8 mg	4.8 mg	8 mg
Prior to interim safety review by DMC: 132 subjects (1:1:1 randomization ratio)	44	44	44	0
Additional subjects randomized while interim safety tables are being generated and reviewed by the DMC (not included in DMC safety interim analysis): 100 subjects (1:1:1 randomization ratio)	34	33	33	0
After interim safety review by DMC: 1081 subjects	270	270	270	270
Total: 1312 subjects	348	347	347	270

[a] Numbers shown for each treatment group are estimates based on randomization ratio. Actual numbers could be slightly different based on randomization block size.

8.2 Populations for Analyses

- The Enrolled Subjects Data Set will consist of all subjects who sign informed consent.
- The Randomized Subjects Data Set will consist of all randomized subjects regardless of whether they received treatment. This is also known as the Intent to Treat (ITT) population. This will be the primary efficacy data set. Data in this data set will be analyzed based on randomized treatment group.
- The Treated Subjects Data Set will consist of all subjects who receive at least one dose of study medication during the treatment period. This will be the primary safety data set. Data in this data set will be analyzed based on randomized treatment, except in the following cases:
  - If a subject received the same incorrect treatment throughout the study (until either Day 28 or Day 90, or until discontinuation of the study drug), then the subject will be analyzed based on the treatment received.
  - If a subject received study drug from more than one treatment group, and none of the administrations were consistent with the assigned randomized treatment group, then the subject will be analyzed based on the first treatment received.

- The Pharmacodynamic analysis dataset will consist of subjects in the Randomized Subject Dataset who have at least one pharmacodynamic endpoint assessed.
- The Pharmacokinetic analysis dataset will consist of all subjects who receive BMS-986141 and have at least one post dose PK sample. Additionally, the evaluable PK population is defined as subjects who have adequate PK profiles on Day 1.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary efficacy endpoint of the study is the incidence of a composite of symptomatic ischemic stroke by Day 28 and unrecognized brain infarction assessed by MRI at Day 28.

8.3.2 Secondary Endpoint(s)

Secondary endpoints include:

- The incidence of major adverse cardiovascular events (MACE) by Day 90, defined as a composite of adjudicated recurrent stroke, myocardial infarction, or CV death
- The incidence of a composite of adjudicated recurrent ischemic stroke, myocardial infarction, or CV death
- The incidence of adjudicated symptomatic recurrent stroke (including fatal and non-fatal) by Day 28
- The incidence of the composite of unrecognized brain infarction assessed by MRI at Day 28 and MACE by Day 90

8.3.3 Exploratory Endpoint(s)

[redacted]

8.3.4 Safety Endpoints

The primary safety endpoint is incidence of a composite of adjudicated major bleeding and adjudicated clinically relevant non-major (CRNM) bleeding during the treatment period.

Additional safety endpoints include the incidence of adjudicated major bleeding events, all bleeding events, intracranial hemorrhage events, as well as the incidence of AEs and markedly abnormal standard clinical laboratory test results.

8.4 Analyses

Adjudicated results will be the basis for the primary and secondary analyses, including imaging assessments from the IAC and clinical assessments from the CEC.

8.4.1 Demographics and Baseline Characteristics

Frequency distributions and summary statistics for demographic and baseline variables will be presented by treatment group and for all subjects combined. Demographic and baseline variables to be summarized include: age, gender, race, geographic region, height, weight, body mass index, vital signs (systolic blood pressure, diastolic blood pressure, and heart rate), index event (stroke or TIA), and cardiovascular risk factors (cigarette smoking, diabetes mellitus, hypercholesterolemia, hypertension, obesity).

Additional baseline variables will include stroke sub-type as assessed by the investigator, severity (NIH-SS), and time since onset of symptoms detected.

In addition, separate summaries taking into account length of treatment (28 or 90 days) and randomization phase (randomized prior to or after DMC safety interim analysis decision) will be provided.

8.4.2 Efficacy Analyses

8.4.2.1 Primary Efficacy Endpoint Analysis

To demonstrate the dose-response relationship between BMS-986141 treatment (including placebo) and primary endpoint, the primary analysis will be based on a Multiple Comparisons and Modeling (MCP-Mod) analysis.[15,16] This analysis tests for a dose-response relationship, allowing for uncertainty in the dose-response relationship through inclusion of contrasts from two pre-specified candidate models to assess dose-response. 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 model, or using a weighted model-averaging method if significance is detected using both models. Candidate models will include an Emax model and a logistic model, where dose-response will be tested using dose levels of 0 (placebo), 1, 2, and 2.3 (corresponding to 0.8 mg, 4.8 mg, and 8 mg)[17]. The parameters used to determine the contrast for testing will include assumed placebo event rate 14% and maximum risk reduction of 4.2%. For the Emax model, the parameters used will be 1.0 for the dose corresponding to half of the maximum effect and 1.0 for a "Hill" parameter that determines the steepness of the model at the dose of half effect. For the logistic model, the initial parameters used will be 1.0 for the dose corresponding to half effect and 0.1 for the parameter that determines the steepness of the curve.

The incidence of the composite of adjudicated symptomatic recurrent ischemic stroke by Day 28 and unrecognized brain infarction at Day 28 will also be summarized by treatment. Point

estimates and 95% CIs for event rates will be presented by treatment, together with point estimates and 95% CIs for the relative risk reduction between each BMS-986141 arm and placebo.

A single categorical variable based on study change points (length of treatment [28 or 90 days] and randomization phase [randomized prior to or after DMC safety interim analysis decision]) will be included as a covariate.

A sensitivity analysis will include subjects who are randomized, treated, and with an evaluable MRI at Day 28, or an adjudicated symptomatic recurrent stroke by Day 28.

8.4.2.2 Secondary Efficacy Endpoint Analyses

Similar analysis methods will be used for the secondary endpoint incidence of MACE as for the primary endpoint.

A sequential testing approach will be used for the primary and MACE endpoints. Dose-response relationship for the primary endpoint will be tested first using a one-sided 0.15 type I error; if the p-value for this comparison is < 0.15, then the dose-response relationship for the same endpoint will be tested using a one-sided 0.025 type I error. If the p-value for this comparison is < 0.025, then the dose-response relationship for the MACE endpoint will be tested using a one-sided 0.025 type I error.

Other secondary endpoints will use similar analysis methods as the primary and secondary endpoint of MACE.

8.4.2.3 Other Efficacy Analyses

Analysis of recurrent ischemic stroke and adjudicated arterial thrombotic events up to 90 days will use similar analysis methods as the primary and secondary endpoint of MACE.

Analyses of exploratory biomarker data are included in Section 8.4.5, Biomarker Analyses.

8.4.3 Safety Analyses

For safety analyses, separate summaries taking into account length of treatment (28 or 90 days) and randomization phase (randomization prior to or after DMC safety interim analysis decision) will be provided.

The proportion of subjects with the composite of major bleeding and CRNM bleeding, and additional bleeding endpoints such as all bleeding events (including major bleeding, clinically relevant non-major bleeding and minor bleeding) and intracranial hemorrhage during the treatment period will be summarized by treatment. Point estimates and 95% CIs for event rates of each of above safety endpoints will be presented by treatment, together with point estimates and 95% CIs for the difference of event rates between each BMS-986141 arm and placebo. A single variable based on study change points (length of treatment [28 or 90 days] and randomization phase [randomized prior to or after DMC safety interim analysis decision]) will be included as a stratum in the calculation of the CIs.

The number and percent of subjects with at least one adverse event will be summarized for each treatment group, including summaries of AEs, SAEs, AEs leading to discontinuation, and AEs of special interest. Summaries will include the number of subjects with events by specified system organ classes and preferred terms. All endpoint events reported by the investigator as AEs (serious or non-serious) will be reported in the safety analyses, regardless of whether the event was confirmed by adjudication. The number and percent of subjects with marked laboratory abnormalities will be similarly presented.

Values and changes from baseline at each scheduled time point for clinical laboratory parameters, vital signs, and ECG will be summarized by treatment group using descriptive statistics.

8.4.4 Pharmacokinetic Analyses

Pharmacokinetics of BMS-986141 and BMT-162856 will be explored.

A population pharmacokinetic model will be developed to understand the pharmacokinetics of BMS-986141. The potential effect of covariates (eg, body weight, age, gender, race, renal function, liver function, co-administration of other medicine) on the pharmacokinetics of BMS-986141 will be also explored. These results will be reported separately.

8.4.5 Biomarker Analyses

Summary statistics will be tabulated for each available biomarker endpoint, including corresponding changes from baseline and/or percentage changes from baseline (where applicable) by treatment, and time point. Plots of means and standard errors over time and change from baseline (and/or percent change from baseline) for each available biomarker versus time may be provided. Relationships between exploratory biomarkers and BMS-986141 plasma concentrations may be explored. In addition, relationships between polymorphism in genes related to PAR4 activity (and/or disposition of BMS-986141) and exploratory biomarkers, PK parameters, or efficacy endpoints may be explored. Exploratory biomarker results may be reported separately.

8.4.6 Outcomes Research Analyses

Not Applicable.

8.4.7 Other Analyses

Exploratory exposure response analysis of pharmacodynamics endpoints driven by BMS-986141 exposure may also be performed and reported separately.

8.5 Interim Analyses

No interim analyses are planned for efficacy. The DMC will, however, review safety data after 10% of the total planned subjects for the study (approximately 132 subjects) have been randomized and have completed their scheduled Day 28 visit. Additionally, pharmacokinetics of BMS-986141 will be explored to assess exposures and potential relationship to safety. Based on the results, the DMC will recommend either to expand randomization to include the higher dose level (8 mg BMS-986141), to maintain randomization for additional subjects to the original three

treatment arms (placebo and the two lower doses), or other modification as necessary to ensure subject safety. Details regarding the safety data to be included in the interim safety analysis will be provided in the DMC Charter. As noted in Section 4.6, information from pharmacokinetic analyses may be made available to non-study team members.

9 STUDY MANAGEMENT

9.1 Compliance

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

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

9.1.2 Monitoring

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

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

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

9.1.2.1 Source Documentation

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

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

9.2 Records

9.2.1 Records Retention

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

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

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

9.2.2 Study Drug Records

Records for IP, eg BMS-986141 or matching placebo, (whether supplied by BMS, its vendors, or the site) must substantiate IP integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

For non-IP supplies, eg ASA, the investigator is not required to maintain records for substantiation of IP integrity and traceability from receipt, preparation, administration, and through destruction or return the non-investigational product.

For ASA, subject level dispensation, administration and drug accountability records are required to ensure patient medication compliance.

If...	Then...
Supplied by BMS (or its vendors):	• Records or logs must comply with applicable regulations and guidelines and should include

If...	Then...
BMS-986141 or matching placebo	• amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
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) Not Applicable for this study, all IP is provided by BMS. See above for instruction for non-IP, Aspirin (ASA)	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

9.2.3 Case Report Forms

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

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

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

9.3 Clinical Study Report and Publications

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

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

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, 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 BMS or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable

Term	Definition
	form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

11 LIST OF ABBREVIATIONS

Term	Definition
ABCD2	neurological assessment scores (age, blood pressure, clinical features, duration, diabetes)
ACS	acute coronary syndrome
AE	adverse event
AF	atrial fibrillation
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASA	acetylsalicylic acid
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(0-24)	area under the concentration-time curve from time zero to 24 hours post dose
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BT	bleeding time
BUN	blood urea nitrogen
C	Celsius
C(24)	concentration at 24 hours
CEC	Clinical Events Adjudication Committee
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CK-MB	creatine kinase- myocardial fraction
cm	Centimeter
Cmax, CMAX	maximum observed concentration
COX-2	cyclooxygenase-2
CRF	Case Report Form, paper or electronic
CRNM	Clinically Relevant Non-Major

Term	Definition
CSF	cerebrospinal fluid
CT	computerized tomography
Ctrough	Trough observed plasma concentration
CV	cardiovascular
CYP	cytochrome P450
D-dimer	fibrin degradation product
D/C	Discontinue
DDI	drug-drug interaction
DILI	drug induced liver injury
dL	Deciliter
DMC	Data Monitoring Committee
DWI	Diffusion-weighted imaging MRI
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	ethylenediaminetetraacetic acid
eg	exempli gratia (for example)
Emax	Asymptotic maximum change from placebo effect
EOT	end of treatment
ESR	Expedited Safety Report
F1.2	F1.2 fragment of prothrombin
FDA	Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
GPIIb/IIIa	glycoprotein IIb/IIIa
h	hour
Hb	hemoglobin
HBsAg	hepatitis B surface antigen
HBV, HepB	hepatitis B virus

Term	Definition
HCG	human chorionic gonadotropin
HCV, HepC	hepatitis C virus
HepA	hepatitis A virus
HIPAA	Health Insurance Portability and Accountability Act
hr, hrs	hour, hours
HR	heart rate
HRT	hormone replacement therapy
IAC	Imaging Adjudication Committee
IB	Investigator Brochure
ICD	International Classification of Diseases
ICF	informed consent form
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
INR	international normalized ratio
IP	investigational product
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
IVRS	Interactive Voice Response System
K	slope of the terminal phase of the log concentration-time curve
K3EDTA	potassium ethylenediaminetetraacetic acid
Kg	kilogram
KIM–1	kidney injury molecule-1
λz	terminal disposition rate constant

Term	Definition
L	liter
LACI	Lacunar infarct
LAM	lactation amenorrhea method
LDH	lactate dehydrogenase
LMWH	low molecular weight heparin
MACE	major adverse cardiovascular events
MAD	multiple-ascending dose
MCP-mod	Multiple Comparison Procedure – Modeling
mg	milligram
MI	myocardial infarction
min	minute
mL	milliliter
mmHg	millimeters of mercury
MRI	magnetic resonance imaging (or image)
μg	microgram
μL	Microliter
N	number of subjects or observations
N/A	Not Applicable
ng	nanogram
NGAL	neutrophil gelatinase-associated lipocalin
NIHSS	National Institutes of Health Stroke Scale
NIMP	non-investigational medicinal products
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drug
OSCP	Oxfordshire Community Stroke Project
PACI	partial anterior circulation infarct
PAR4	protease-activated receptor-4
PD	pharmacodynamics
PK	pharmacokinetics
PO	per os (by mouth route of administration)

Term	Definition
POCI	posterior circulation infarct
PT	prothrombin time
PTT	partial thromboplastin time
QC	quality control
QD, qd	quaque die, once daily
R^2	coefficient of determination
RBC	red blood cell
SAD	single ascending dose
SAE	serious adverse event
sCD40L	soluble CD40 ligand
SD	standard deviation
SI	International system of units
SOP	Standard Operating Procedures
sP-selectin	soluble P-selectin
T1WI	T1-weighted images
T2WI	T2-weighted images
TACI	Total anterior circulation infarct
TAT	thrombin-antithrombin III
TB	total bilirubin
T-HALF	Half life
TIA	transient ischemic attacks
TSH	thyroid stimulating hormone
Tx	Treatment
ULN	upper limit of normal
US	Ultrasound
VTE	venous thromboembolism
WOCBP	women of childbearing potential
wt	Weight

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APPENDIX 1 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

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

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

- 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.

At a minimum, subjects must agree to use one highly effective OR one less effective method of contraception as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Contraception methods are as follows:

1. Nonhormonal IUDs, such as ParaGard®
2. Bilateral tubal occlusion
3. Vasectomised partner with documented azoospermia 90 days after procedure
    a. Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
4. Complete abstinence
    a. Complete abstinence is defined as the complete avoidance of heterosexual intercourse. (refer to Glossary of Terms)

b. Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the investigational drug plus 30 days).
c. It is not necessary to use any other method of contraception when complete abstinence is elected.
d. Subjects who choose complete abstinence must continue to have pregnancy tests.
e. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
f. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

LESS EFFECTIVE METHODS OF CONTRACEPTION

1. Diaphragm with spermicide
2. Cervical cap with spermicide
3. Vaginal sponge with spermicide
4. Male or female condom with or without spermicide*

* A male and a female condom must not be used together.

UNACCEPTABLE METHODS OF CONTRACEPTION

1. Periodic abstinence (calendar, symptothermal, post-ovulation methods)
2. Withdrawal (coitus interruptus)
3. Spermicide only
4. Lactation amenorrhea method (LAM)

Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug.

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

REFERENCES FOR THE USE OF CONDOMS WITH SPERMICIDE.

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Protocol Number: CV006004
IND Number: 122,675
EUDRACT Number 2015-003959-22
Date: 07-Jul-2016

Protocol CV006004: A Phase 2, Placebo Controlled, Double-Blind, Parallel-Arm Study to Evaluate Efficacy and Safety of BMS-986141 For the Prevention of Recurrent Brain Infarction in Subjects receiving acetylsalicylic acid (ASA) following Acute Ischemic Stroke or Transient Ischemic Attack

Amendment Number 06
Site Number: All

Study Director

Principal Investigator

Medical Monitor
Fraz Ismat, M.D.

24-hr Emergency Telephone Number:

Bristol-Myers Squibb Research and Development

This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).

This amendment must be maintained with the referenced protocol.

Amendment Rationale:

The purpose of this amendment is to implement changes to several aspects of the study that are intended to further ensure the safety of subjects participating in the study. Changes to the protocol are being implemented before any subjects have been enrolled.

These changes are being made in response to recent data from a 90 day toxicology study in monkeys that showed moderate degeneration/regeneration of the tubular epithelium of the kidneys with pale eosinophilic material and multinucleated giant cells at 75 mg/kg/day (approximately 4 x the projected AUC in subjects at 16 mg QD). Full recovery of the renal pathology was evident after a 1-month post-dose evaluation. Refer to the BMS-986141 Investigator Brochure, Version 3 for additional information.

This amendment modifies the study design to allow initiation of the study with subjects being randomized to placebo, 0.8, or 4.8 mg BMS-996141, with no subjects randomized to the top dose until after a DMC review of safety and laboratory data from the Day 28 study visit for at least 10% of the planned total subjects. In addition, after this review the top dose will be 8 mg of BMS-986141 instead of 16 mg. Changes have also been made to exclusion criteria related to renal function and factors that may influence exposures to the drug, as well as to criteria that require discontinuation of subjects who are on treatment. Guidance around the use of CYP3A4 inhibitors has been further clarified as the use of CYP3A4 substrates may increase concentrations of BMS-986141. In addition, the laboratory tests included in the study have been modified to include urinalysis at all treatment period visits and the assessment of renal biomarkers to more closely assess renal function of the study subjects. The statistical section and sample size calculations have been updated to correspond to these changes.

Additional changes include: expansion of time windows for PK sample collection to reduce challenges in collecting samples when subjects are randomized outside of routine working hours; changing requirements for contraception to allow the use of one highly effective method of contraception or one less effective method of contraception to be consistent with BMS SOPs as BMS-986141 is currently considered unlikely to be a teratogen since BMS-986141 produced no developmental toxicity in rats and rabbits when dosed up the maximal feasible dose, 150 mg/kg/day, in expanded range-finding studies; clarified that women enrolled in the study cannot use hormonal contraception as their sole means of contraception; added a statement in Appendix 1 that local laws and regulations may require use of alternative and/or additional contraception methods; added pregnancy test to be done at Day 90 in Part 2; clarified genotyping testing to include the types of genes that will be studied and the location and duration of sample storage; updated protocol to provide further clarifications to assist with study implementation and reflect recent changes in the BMS protocol model document template; corrected typographical errors.

This protocol amendment applies to all subjects to be enrolled in the study.

Changes to the Protocol:

1. Synopsis, Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s)
   a) All treatments: removed approximate number of subjects per treatment arm
   b) Treatment D: dose changed from 16 mg QD to 8 mg QD
2. Synopsis, Study Design
   a) Removed the randomization ratio
   b) Added text stating that initially randomization will be limited to the placebo and the two lower dose treatment groups (0.8 mg QD and 4.8 mg QD), randomization to the highest dose treatment arm (8 mg) will only be initiated after DMC review of safety data from the Day 28 study visit for at least 10% of the planned total subjects.
   c) Study Schematic:
      i) Parts 1 and 2 - changed 16.0 mg dose group to 8.0 mg; added note that 8 mg dose group will only be initiated after DMC review of initial safety
      ii) Part 1 - updated Day 28 to clarify this is end of treatment.
3. Synopsis, Study Assessments, Safety: Added text describing that initially randomization will be limited to the placebo and two dose lower treatment groups (0.8 mg QD and 4.8 mg QD) with no randomization to the 8 mg dose. Randomization to the 8 mg treatment arm will only be initiated after DMC review of safety data from at least 10% of the planned total subjects that have completed their scheduled Day 28 visit. As a result of this review, the DMC can recommend expansion of the randomization to all 4 study arms or other modifications as needed to ensure subject safety.
4. Synopsis, Statistical Considerations, Sample Size: Updated paragraph to state that initially randomization will be limited to the placebo, 0.8 and 4.8 treatment groups until DMC review of the Day 28 safety data from the first 10% of subjects. Initially, the randomization will be in a 1:1:1 ratio. If the DMC recommends proceeding to the inclusion of the highest dose group the randomization ratio will then become 1:1:1:1. Changed the 16 mg dose group to 8 mg.
5. Synopsis, Primary Efficacy Endpoint Analysis: update text of 3rd bullet to state that a single categorical variable based on study change points (length of treatment [28 or 90 days] and randomization phase [randomized prior to or after DMC safety interim analysis decision]) will be included as a covariate.
6. Synopsis, Safety Analysis:
   a) Added a new 1st bullet to state that for safety analyses, separate summaries taking into account length of treatment (28 or 90 days) and randomization phase will be provided.
   b) Former 1st bullet, now 2nd bullet: added text at the end of the paragraph to state that a single categorical variable based on study change points (length of treatment [28 or 90 days] and randomization phase [randomized prior to or after DMC safety interim analysis decision]) will be included as a stratum in the calculation of the CIs.
7. Section 1.3.4, Exploratory Objectives

[redacted]

8. Section 1.4.1 Clinical Pharmacology and Safety
   a) 1st paragraph, 1st sentence: updated number of subjects that received single doses in the study
   b) 2nd paragraph, 1st sentence: added BUN and creatinine.
9. Section 1.5, Overall Risk/Benefit Assessment, 3rd paragraph
   a) after first sentence added information from the 3 month toxicity studies in monkeys.
   b) Previous 2nd sentence and information that follows becomes new 4th paragraph.
10. Section 3.1, Study Design and Duration,
   a) 2nd paragraph, removed randomization ratio and number of subjects per treatment arm.
   b) 3rd paragraph, 1st sentence: update to state the 90 day non-clinical toxicology studies were recently completed.
   c) Study Schematic:
      i) Parts 1 and 2 - changed 16.0 mg dose group to 8.0 mg; added note that 8 mg dose group will only be initiated after DMC review of initial safety.
      ii) Part 1 - updated Day 28 to clarify this is end of treatment.
11. Section 3.3.1, Inclusion Criteria
   a) 1a: added note that consent by a LAR will only be allowed if permitted by local regulations.
   b) 3a: updated to state subjects must be a minimum of 18 years old or age of majority (if local age of majority is >18 years of age) to participate in the study as per the model document.
   c) 3g: added criterion to state that women of child-bearing potential who use hormonal contraception must agree to use an additional method of birth control but female partners of male subjects may use hormonal contraceptives as they are not taking study medication.
   d) 3, 2nd paragraph after lettered list: changed to state, at a minimum subjects must use one highly effective method of contraception OR one less effective method.
   e) 3rd, paragraph: All text related to contraceptive methods is removed from protocol and now in Appendix 1 as per the model document.
   f) Added a statement in Appendix 1 that local laws and regulations may require use of alternative and/or additional contraception methods.
12. Section 3.3.2, Exclusion Criteria
   a) 2c: added that subjects with acute gastrointestinal ulcers are to be excluded from the study.
   b) 2f: changed to exclude subjects with moderate or severe hepatic impairment, defined as Child-Pugh Class B or C, and added reference to Appendix 5.
   c) 2g: changed to exclude subjects with moderate to severe renal impairment defined as an estimated glomerular filtration rate (eGFR)< 45 mL/min.
   d) 2o: added exclusion of subjects who have received intravenous or intra-arterial thrombolysis or mechanical thrombectomy within the past 48 hours or who are currently eligible and able to receive these treatments for their current stroke.
   e) 3a, v): removed exclusion of QTcF≥ 450 msec as these subjects are expected to be excluded based on uncorrected QT interval

f) 6e: deleted this exclusion as it is now addressed in exclusion criteria 2o.

g) 6g: added that use of strong CYP3A4 inhibitors or strong CYP3A4 inducers are prohibited in the 7 days prior to randomization and during the study.

13. Section 3.3.3, Women of Childbearing Potential: Section deleted. This information is now in Appendix 1.

14. Section 3.4.1, Prohibited and/or Restricted Treatments

a) 2nd paragraph, first bullet: added that low molecular weight heparin (LMWH) can be used to maintain patency of indwelling catheters or for prophylaxis of VTE.

b) 2nd paragraph, third bullet: deleted any intravenous or intra-arterial thrombolysis as this is more clearly stated in exclusion criterion 2o) above

c) 2nd paragraph, 4th bullet: updated to state that concomitant oral or intravenous therapy with strong CYP3A4 inhibitors or inducers is prohibited.

d) 5th paragraph: added that subjects requiring treatment with strong CYP3A4 inhibitors or strong CYP3A4 inducers must be discontinued from study treatment and that is recommended the CYP3A4 inhibitor or inducer is not started for at least 24 hours after the last dose of study medication.

15. Section 3.5, Discontinuation of Subjects following an Treatment with Study Drug

a) 6th bullet: deleted that subjects will be discontinued if unblinded for any reason, as per the model document

b) 10th bullet: Changed definition of severe renal impairment to severe or moderate renal impairment with a eGFR<45 mL/min for more than 7 days.

c) added 12th bullet: added that subjects requiring treatment with strong CYP3A4 inhibitors or strong CYP3A4 inducers will have study treatment discontinued.

d) added 13th bullet: added that subjects treated with any intravenous or intra-arterial thrombolysis or mechanical thrombectomy will be discontinued from study treatment

e) 3rd paragraph: wording changes per new protocol model document. Reference to BMS Medical Monitor changed to Sponsor or designee and 2nd sentence deleted.

16. Section 4.3, Storage of Study Drug and Dispensing:

a) Section title changed to 4.3 Storage of Study Drug

b) 3rd paragraph deleted per the model document

c) Added new 3rd paragraph referencing Section 9.2.2 for guidance on IP records and documentation.

17. Section 4.4, Method of Assigning Subject Identification, 2nd paragraph:

a) changed 16 mg treatment group to 8 mg

b) added that randomization will be limited to the two lower doses of BMS-986141 or placebo in a 1:1:1 ratio until after DMC review of safety and laboratory data from the Day 28 study visit for at least 10% of the planned total subjects. If the DMC recommends proceeding to inclusion of the highest dose, subsequent randomization will be in a 1:1:1:1 ratio.

18. Section 4.5, Selection and Timing of Dose for Each Subject, 3rd paragraph. Updated to note that initially each daily dose of study medication will consist of 4 tablets, however, drug supplies that may be available in early 2017 may allow for dosing with 2 tablets daily. Sites

will be provided with instructions and guidance on how to implement this change if it is to occur.

19. Section 4.6, Blinding/Unblinding
    a) 7th paragraph: added that designated senior staff of BMS Research and Development independent from the study oversight team will be unblinded to pharmacokinetic results and may make recommendations to enroll additional participants to specific dosage tiers in order to obtain sufficient exposures. Any such recommendations will be considered by the Steering Committee and DMC.
    b) 8th paragraph: added that the pharmacokineticist or designate in Clinical Pharmacology and Pharmacometrics; and programmers in Data Sciences may be unblinded in order to prepare preliminary summaries of pharmacokinetic, and safety data, as needed before data is more generally unblinded.
    c) 10th paragraph: clarified that a BMS biomarker representative and/or their designate may be unmasked to review the platelet aggregation data.
20. Section 4.8, Destruction of Study Drug:
    a) Section title changed to 4.8 Destruction or Return of Investigational Product;
    b) added table after 1st paragraph providing guidelines for investigational product destruction;
    c) content of this section has been rearranged per the model document.
21. Section 4.9, Return of Study Drug: section deleted and text moved to Section 4.8 per model document
22. Section 4.10, Retained Samples for Bioavailability/Bioequivalence: section number changed to 4.9.
23. Section 5.1 Flow Chart/Time and Events Schedule
    a) Table 5.1-1, Screening Procedural Outline
        i) Local Laboratory Tests: clarified all screening laboratory tests are analyzed locally
        ii) Follicle Stimulating Hormone (FSH) Test: clarified this is only done for post-menopausal women under the age of 55
        iii) Deleted comment for Urinalysis
        iv) TSH testing deleted as there were no increases in TSH observed in the phase 1 study of BMS-986141
    b) Tables 5.1-2 and 5.1-3, Part 1 and Part 2 Procedural Outlines
        i) Central Laboratory: clarified that chemistry and hematology samples will be sent to the central laboratory for analysis throughout the study.
        ii) Added Urinalysis tests, to be done locally, at the Day 1, Day of Hospital Discharge and Day 28 visits (and Day 56 and Day 90 for Part 2).
        iii) Deleted TSH testing
        iv) Serial/Sparse Blood PK Sampling and Platelet Aggregation: updated collection window for Day 1 24 hour post-dose PK sample

v) [redacted]

vi) [redacted]

vii) Pregnancy Test, Part 2, Day 90: Added an additional X and comment to indicate the a pregnancy test must be done at the Day 90 visit in addition to the home test done at Day 84.

24. Section 5.3.7, Laboratory Test Assessments:
    a) Inserted new paragraph between paragraphs 1 and 2 to clarify that unexpected abnormal results on urinalysis should be confirmed by retesting a new, carefully obtained sample.
    b) 4th paragraph, clarified that any abnormal laboratory test will evaluated as clinically indicated.
25. Table 5.3.7-1, Laboratory Assessments:
    a) Deleted bicarbonate testing at Screening
    b) Clarified FSH is only done for post-menopausal women under the age of 55
    c) Deleted TSH testing
    d) Clarified urinalysis will be done locally at all required time points
26. Section 5.4.1, Symptomatic Stroke, 2nd paragraph, 1st sentence: clarified requirements for diagnosis of stroke
27. Table 5.5-1: Pharmacokinetic Sampling Schedule: updated the sample collection windows for the Day 1 - 8 hr and Pre-dose Day 2 (Day 1-24 hr) samples.
28. Section 5.6.1, Exploratory Biomarker Assessments:

[redacted]

29. Section 5.8.2, ABCD2: clarified this will be source document

30. Section 6, Adverse Events; Section 6.1.1, Serious Adverse Event Collection and Reporting; Section 6.4, Pregnancy; Section 9.2.3, Case Report Forms; Section 9.3, Clinical Study Report and Publications
    a) Changed BMS or BMS Medical Monitor to Sponsor or designee as per the model document
31. Section 6.4, Pregnancy, 5th paragraph: clarified that a pregnancy in a female partner of a male study subject will require the female partner to provide informed consent to disclose pregnancy related information.
32. Section 7.1, Data Monitoring Committee: added 2nd paragraph describing that the DMC will review the safety data from the at least 10% of the total planned subjects randomized to the 0.8, 4.8 or placebo groups and will make their recommendation before randomizations to the 8 mg treatment arm can begin.
33. Section 8.1, Sample Size Determination
    a) 1st paragraph, 3rd sentence: changed 16 mg dose to 8 mg
    b) Updated 2nd paragraph to describe randomizations ratios and sample size calculations based on the possible staggered randomization from 3 treatment groups to 4 treatment groups.
    c) Added Table 8.1-1: Randomization Targets
34. Section 8.3.3 Exploratory Endpoint(s):
    a) 2nd bullet: Deleted NR-2 peptide
    b) Added 3rd bullet to state change from baseline on renal biomarkers is a new exploratory endpoint
    c) former 3rd bullet, now 4th bullet: added that polymorphisms in genes related to platelet activity will also be studied.
35. Section 8.4.1 Demographics and Baseline Characteristics
    a) 2nd paragraph: deleted summaries of baseline variable by study phase
    b) added 3rd paragraph stating separate summaries taking into account the length of treatment and randomization phase will be provided.
36. Section 8.4.2.1, Primary Efficacy Endpoint Analysis:
    a) 1st paragraph, 4th sentence: updated the dose levels to reflect change from 16 mg to 8 mg treatment arm.
    b) 3rd paragraph: deleted.
    c) new 3rd paragraph added to address new covariate.
37. Section 8.4.3, Safety Analyses:
    a) Added new 1st paragraph describing that for safety analyses separate summaries taking into account length of treatment and randomization phase will be provided.
    b) 1st paragraph (now 2nd paragraph): added a 3rd sentence stating that a single variable based on study change points (length of treatment and randomization phase) will be included as a stratum in the calculation of the CIs.
    c) 2nd paragraph (now 3rd paragraph): delete 4th sentence stating AE summaries will be presented by treatment length.

38. Section 8.4.4, Pharmacokinetic Analyses, 1st paragraph: deleted reporting of Cmax, AUC(0-24), C(24) after first dose, and C(24) on Day 28 due to the need to expand PK sample collection windows.
39. Section 8.5, Interim Analyses: Updated to state no interim analyses are planned for efficacy. Description of review of safety data after 10% of the total planned subjects for the study have completed the Day 28 visit and that pharmacokinetics will be explored to assess exposure.
40. Section 9.1.1, Compliance with Protocol and Protocol Revisions
    a) Deleted 1st sentence as per the model document
    b) 1st paragraph, 2nd sentence: added statement that if applicable, local health authority of approval/favorable opinion must be received prior to implementing a protocol amendment and additional wording changes per the model document
    c) 2nd paragraph: updated wording per the model document
    d) 3rd paragraph: added statement that if applicable, local health authority of approval/favorable opinion must be sent to BMS
41. Section 9.1.2, Monitoring
    a) Reference to BMS changed to BMS or designee per the model document
42. Section 9.1.3, Investigational Site Training
    a) Section deleted per the model document
43. Section 9.2.1 Records Retention
    a) 1st paragraph: added that investigator or head of study site in Japan must retain all study all study records
    b) All paragraphs: changed BMS to BMS or designee per the model document
44. Section 9.2.2, Study Drug Records:
    a) Clarified that records for IP, eg, BMS-986141 or matching placebo must be maintained as described in this section. Clarified ASA is considered non-IP and described the records that must be maintained for ASA.
    b) Table inserted that describes the records required to be maintained
    c) Added statement that sites are not required to retain records that substantiate IP integrity and traceability from receipt, preparation, administration, and through destruction or return of the non-investigational product, ASA used in this study. Subject level administration and drug accountability records are required.
    d) additional wording updated per the model document
45. Section 9.2.3, Case Report Forms, 5th paragraph: Added that subinvestigators in Japan may not be delegated the CRF approval task as per the model document
46. Section 11, List of Abbreviations
    a) Deleted NR2 peptide
    b) Added: KIM-1, NGAL,
47. Added the following Appendices:
    a) Appendix 1, Women of Childbearing Potential Definitions and Methods of Contraception
    b) Appendix 2 - NIH Stroke Scale
    c) Appendix 3 - ABCD^2 Assessment Source Document

d) Appendix 4 - Oxfordshire Community Stroke Project Classification
e) Appendix 5 - Child-Pugh Classification Criteria

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.

AMENDMENT ACKNOWLEDGMENT

I have read this Amendment and agree that it contains all necessary details for carrying out the changes described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion by all necessary Health Authorities before implementation unless to eliminate an immediate hazard to subjects.

If this Amendment substantially alters the study design or increases potential risk to subjects, the consent form will be revised and submitted to the Institutional Review Board/Independent Ethics Committee for approval/positive opinion. I will use the new consent form for any new subjects prior to enrollment, and for subjects currently enrolled in the study if they are affected by the Amendment.

_____ _____
Investigator's printed name and signature *Date*

_____ _____
Medical Monitor/Study Director *Date*
(If required by applicable regulations and guidelines.)

Protocol Number: CV006004
Site Number:
Amendment Number: 06