STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

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

PROTOCOL(S) CV006004

VERSION # 1.0

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN FOR CLINICAL STUDY REPORT 1
TABLE OF CONTENTS 2
LIST OF TABLES 5
LIST OF FIGURES 6
1 BACKGROUND AND RATIONALE 7
2 STUDY DESCRIPTION 8
2.1 Study Design 8
2.2 Treatment Assignment 9
2.3 Blinding and Unblinding 10
2.3.1 Blinding 10
2.3.2 Unblinding 11
2.4 Protocol Amendments 11
3 OBJECTIVES 11
3.1 Primary 11
3.2 Secondary 11
3.3 Safety 12
3.4 Exploratory 12
4 ENDPOINTS 12
4.1 Primary Efficacy Endpoint 12
4.1.1 Symptomatic Stroke 12
4.1.2 Unrecognized Brain Infarction 13
4.2 Secondary Efficacy Endpoints 13
4.3 Exploratory Endpoints 13
4.4 Primary Safety Endpoint 14
4.5 Additional Safety Endpoints 14
5 SAMPLE SIZE AND POWER 14
6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES 15
6.1 Study Periods 15
6.2 Treatment Regimens 15
6.3 Populations for Analyses 15
7 STATISTICAL ANALYSES 16

7.1 General Methods 16
7.1.1 General Methods for Study Periods *16*
7.1.2 General Methods for Efficacy Analyses *17*
7.2 Study Conduct 19
7.2.1 Accrual *19*
7.2.2 Relevant Protocol Deviations *19*
7.3 Study Population 20
7.3.1 Subject Disposition *20*
7.3.2 Demographic and Baseline Characteristics *20*
7.3.3 Medical History *21*
7.4 Extent of Exposure 21
7.4.1 Administration of Study Therapy *21*
7.4.2 Study Therapy Compliance *21*
7.4.3 Modifications of Study Therapy *22*
7.4.4 Concomitant Medications *22*
7.5 Efficacy 22
7.5.1 Primary Efficacy Analysis *22*
7.5.1.1 Sensitivity Analyses *23*
7.5.1.2 Subgroup Analyses *23*
7.5.2 Secondary Efficacy Analyses *24*
7.5.3 Other Efficacy Analyses *25*
7.6 Safety Analyses 25
7.6.1 Major Bleeding and Clinically Relevant Non-Major Bleeding *25*
7.6.2 Deaths *26*
7.6.3 Serious Adverse Events *26*
7.6.4 Adverse Events *26*
7.6.5 Clinical Laboratory Evaluations *27*
7.6.6 Electrocardiograms *28*
7.6.7 Vital Signs *28*
7.6.8 Physical Examination Findings *29*
7.7 Pharmacokinetic Analyses 29
7.8 Biomarker Analyses 29
8 CONVENTIONS 30

8.1 Decimal Places 30
8.2 Pharmacokinetic Summaries 30
8.3 Day Ranges for Analysis of Time Points 30
8.4 Multiple Measurements 31
9 CONTENT OF REPORTS 32
APPENDIX 1 MARKED ABNORMALITY CRITERIA FOR LABORATORY TEST RESULTS - CONVENTIONAL (US) UNITS 33
APPENDIX 2 MARKED ABNORMALITY CRITERIA FOR LABORATORY TEST RESULTS -- SI UNITS 37
10 REFERENCES 41

LIST OF TABLES

Table 5-1: Randomization Targets 14
Table 7.2.2-1: List of Relevant Protocol Deviations 19
Table 7.4.1-1: Extent of Exposure Categories for Summarization 21
Table 7.5.1.2-1: Subgroups of Interest for Efficacy Assessments 23
Table 7.6.7-1: Out of Range Vital Signs Criteria 29
Table 8.3-1: Analysis Windows for Laboratory Parameters & Vital Signs (Part 1) 31
Table 8.3-2: Analysis Windows for Laboratory Parameters & Vital Signs (Part 2) 31
Table 8.3-3: Analysis Windows for ECG Results 31

LIST OF FIGURES

Figure 2.1-1: Study Design Schematic for Part 1.....9
Figure 2.1-2: Study Design Schematic for Part 2.....9

1 BACKGROUND AND RATIONALE

[redacted]

[redacted]

Research Hypothesis:

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

Schedule of Analyses:

No interim analyses are planned to assess 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. There are no other planned interim analyses for this study.

The final analyses for the clinical study report will be performed following the database lock after all subjects have completed the study.

2 STUDY DESCRIPTION

2.1 Study Design

This study is a randomized, double-blind, placebo-controlled, parallel arm clinical trial in subjects receiving acetylsalicylic acid (ASA) with a recent Acute Ischemic Stroke (AIS) or Transient Ischemic Attack (TIA).

The study consists of two parts. Part 1 will have a treatment duration of 28 days. Part 2 will begin once results from ongoing toxicology studies are reviewed, and will have a treatment period of 90 days. Subjects enrolling in Part 1 will not be allowed in Part 2. The figures below illustrate the treatment plan for both study parts.

Figure 2.1-1: Study Design Schematic for Part 1

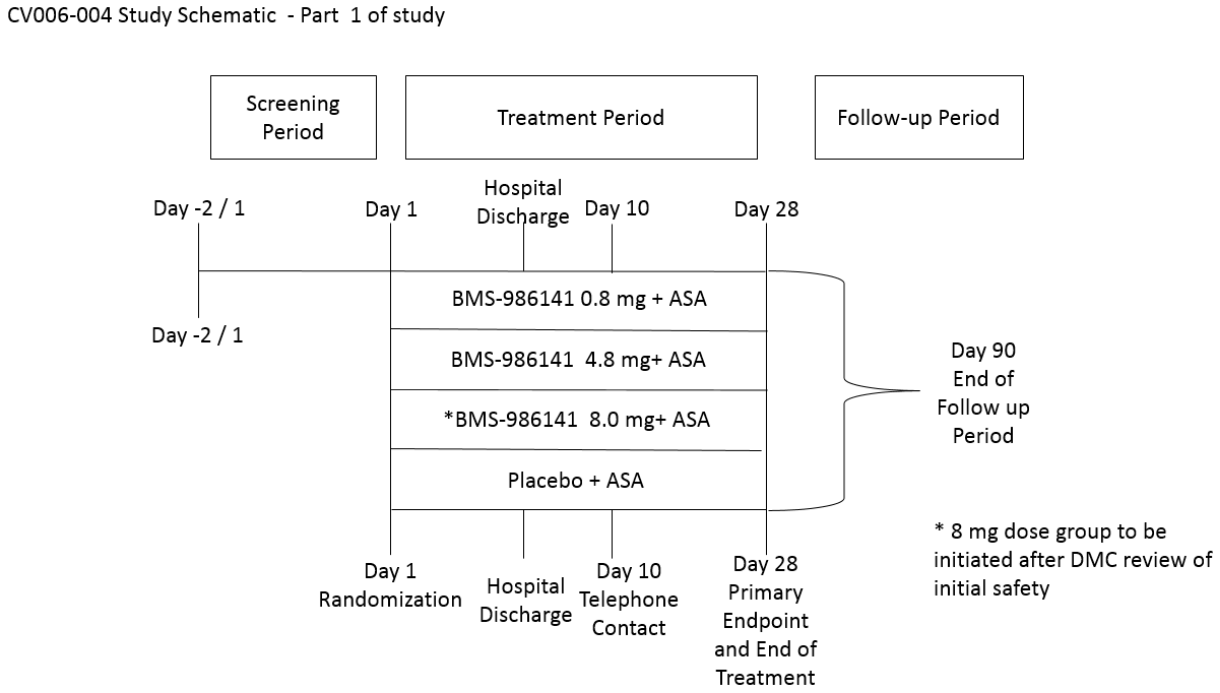
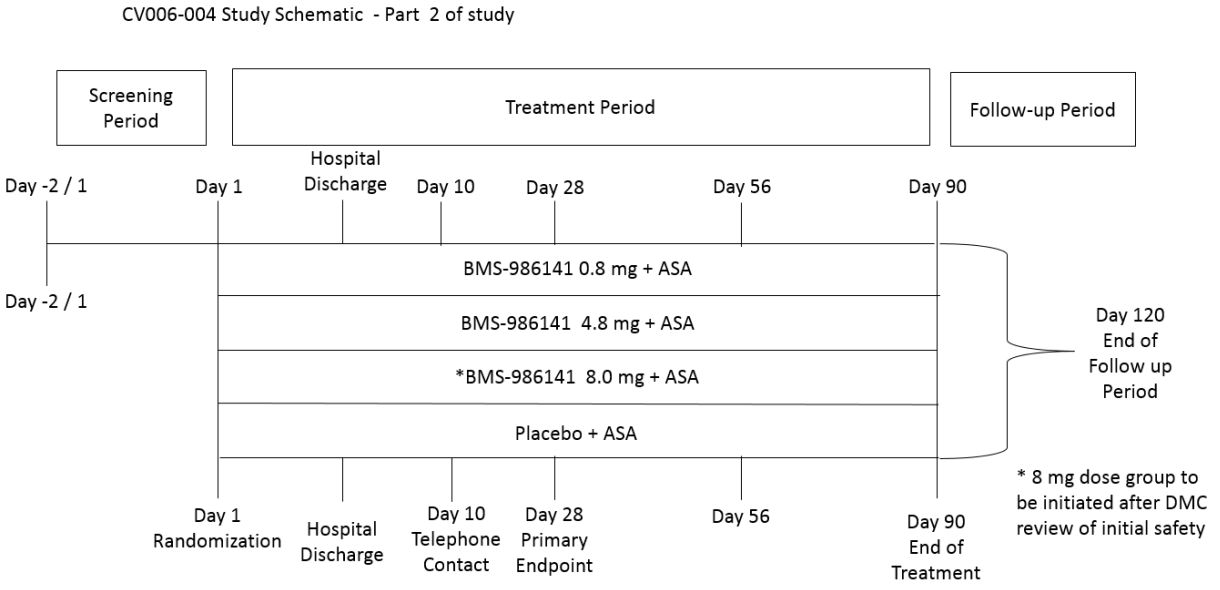


Figure 2.1-2: Study Design Schematic for Part 2



2.2 Treatment Assignment

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%.

In addition to the two Parts of the study noted above, which are related to treatment duration, the study also consists of two phases, each with a slightly different method of assigning study treatment. In Phase A, subjects will be randomized 1:1:1 using IVRS to one of two doses of BMS-986141 (0.8 mg or 4.8 mg) or placebo. In Phase B, subjects will be randomized 1:1:1:1 via IVRS to one of three doses of BMS-986141 (0.8 mg, 4.8 mg, or 8 mg) or placebo. The transition from Phase A to Phase B of the study will only occur after an Independent Data Monitoring Committee (DMC) has reviewed data from the first 10% of the planned subjects (approximately 132 subjects with 28 days of data). As of the time of the writing of this SAP, the decision to move from Part 1 to Part 2 of the study has been made. Some sites will continue to enroll subjects in to Part 1 of the study until Part 2 can be fully implemented. As a result, there will be no subjects randomized in Phase B during Part 1 of the study.

Randomization schedules will be generated by BMS and kept by the IVRS vendor. All subjects will receive open-label ASA at a dose from 75 to 162 mg per day beginning at a time consistent with local standards of care for patients with AIS or TIA. As mentioned in section 2.1, the planned study dosing duration is 28 days for Part 1 of the study and 90 days for Part 2 of the study.

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.

2.3 Blinding and Unblinding

2.3.1 Blinding

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the investigational product is critical to the subject's management, procedures are in place to have the blind broken for an individual subject.

Except as noted, BMS Research and Development personnel, as well as all vendors responsible for the conduct of the trial (protocol team) will remain blinded for the duration of the trial. The Data Monitoring Committee (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. This unblinded analysis team will not provide any information from unblinded analyses to the protocol team until after the trial has been completed.

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 has been completed.

Platelet aggregation data 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, 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 trial has been completed.

2.3.2 Unblinding

For this study, the method of unblinding for emergency purposes is IVRS. Details are included in the IVRS manual.

2.4 Protocol Amendments

A protocol revision was formally issued on 07-July-2016, incorporating several design changes into the study. Most notably, the original planned high dose of BMS-986141 was reduced from 16 mg to 8 mg, and this arm of the study is to be closed off until the Data Monitoring Committee is able to evaluate sufficient safety data from the 2 lower dose groups (0.8 mg and 4.8 mg). To that effect, the randomization scheme was updated to keep the 8mg arm closed until the DMC convened. Pending the outcome of the DMC meeting, the 8mg arm would open and randomization would proceed in a 1:1:1:1 fashion from there forward to one of the three BMS-986141 doses or placebo (see Table 5-1).

Additional updates were made to clarify various aspects of the study and can be found in the protocol revision. No further updates had a significant impact to the statistical methods planned for this study.

3 OBJECTIVES

3.1 Primary

The primary objective of the study 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 and unrecognized brain infarction as assessed by MRI in subjects with ischemic stroke or TIA treated with ASA.

3.2 Secondary

- 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

3.3 Safety

- 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

3.4 Exploratory

- [redacted]

4 ENDPOINTS

4.1 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. Each of these will be assessed by an adjudication committee. If a subject experiences any of these events, the subject will be counted as having experienced a composite event in the analysis.

In the event that one, but not both of the components of the primary endpoint cannot be ascertained, then the remaining component will be evaluated. In this case, if the remaining component is counted as an event, the composite event will be considered as having occurred. If, however, the remaining component is not counted as an event, or if both of the components of the primary endpoint cannot be ascertained, the resulting primary endpoint will be considered as missing.

4.1.1 Symptomatic Stroke

All cases of suspected recurrent stroke will be adjudicated by a blinded Clinical Events Adjudication Committee (CEC). Diagnosis of stroke will require the abrupt onset of focal

neurological symptoms lasting at least 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.

4.1.2 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. The baseline and Day 28 MRIs for each subject will be reviewed independently by the blinded neuroradiologists of the Imaging Adjudication Committee (IAC) 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.

4.2 Secondary Efficacy Endpoints

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 cardiovascular-related death (CV death)
- The incidence of a composite of adjudicated recurrent ischemic stroke, myocardial infarction, or CV death by Day 90
- 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

Myocardial Infarction and cardiovascular death will be adjudicated by the Clinical Events Adjudication Committee (CEC). As the composite secondary endpoints are each defined in the list above, if a subject experiences any of these events, the subject will be counted as having experienced a composite event in the analysis.

4.3 Exploratory Endpoints

[redacted]

- [redacted]

4.4 Primary Safety Endpoint

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. If a subject experiences any of these events, the subject will be counted as having experienced a composite event.

4.5 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. As well, vital signs, ECG results, physical exam findings, and certain renal parameters and biomarkers, including estimated glomular filtration rate (eGFR), Cystatin-C, NGAL, and KIM-1 may be considered as additional safety endpoints.

5 SAMPLE SIZE AND POWER

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[4]. 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 the 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 in the table below 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 5-1: Randomization Targets

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

Table 5-1: Randomization Targets

	Placebo	0.8 mg	4.8 mg	8 mg
subjects (1:1:1 randomization ratio)				
After interim safety review by DMC: 1081 subjects	270	270	270	270
Total: 1312 subjects	348	347	347	270

Note: Numbers shown for each treatment group are estimates based on randomization ratio. Actual numbers could be slightly different based on randomization block size and rate of enrollment.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

As outlined in section 2.1, the study will be conducted in two parts.

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 are currently ongoing. 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.

Periods for each part of the study include pre-treatment, on-treatment, and post-treatment. Schematics for each study part are provided in Section 2.1.

6.2 Treatment Regimens

Study treatments will be assigned according to the details provided in section 2.2 of this SAP.

6.3 Populations for Analyses

The analyses will use several populations as defined below.

1) All Enrolled Subjects: Includes all subjects who signed informed consent.
2) All Randomized Subjects / Intent to Treat (ITT) Population: Includes all subjects who were randomized to a treatment, regardless of whether they received study drug or not. This population will be analyzed according to the treatment assigned at randomization.
3) All Evaluable Subjects: Includes All Randomized Subjects as above, excluding those subjects' visits where relevant protocol deviations occurred, as defined in Section 7.2.2.
4) All Treated Subjects: Includes all subjects who received at least one dose of study medication. This will be the primary population used in safety analyses and will be analyzed according to the treatment assigned at randomization, except in the following cases:
   - If a 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.

5) Pharmacodynamics (PD) Population: A subset of the ITT Population that includes subjects with at least one pharmacodynamic endpoint assessed following the first dose of BMS-986141.
6) Pharmacokinetic (PK) Population: Includes all subjects treated with BMS-986141 who also have at least one post-dose PK sample. The Evaluable PK Population is further defined as a subset of the PK Population including subjects who have adequate PK profiles on Day 1.

7 STATISTICAL ANALYSES

SAS® version 9 or higher will be used for statistical analyses, tabulations and graphical presentations. The DoseFinding package for R (version 3.1.3 or higher) will also be used in the conduct of the multiple comparisons modelling analyses.

7.1 General Methods

Descriptive summaries will be presented for continuous variables using number of subjects (N), mean, standard deviation (SD), median, minimum and maximum. Geometric mean and coefficient of variation (%CV) will also be presented for sample plasma concentration-time data and PK parameters. Descriptive summaries for categorical variables will utilize counts and percentages.

Adverse events will be coded according to the most recent Medical Dictionary for Regulatory Activities (MedDRA) version. Adverse events will be summarized according to the MedDRA coded Preferred Terms (PT) by System Organ Class (SOC). Previous and concomitant medications will be coded using the WHO Drug Dictionary version.

Unless otherwise specified, baseline is defined as the last non-missing result with a collection date-time prior to the date-time of the first active dose of study medication.

7.1.1 General Methods for Study Periods

Given the different planned study treatment durations between Part 1 (treatment duration of 28 days) and Part 2 (treatment duration 90 days) and time at which randomization will be extended to include the high dose of BMS-986141 (8 mg) following review of safety data by the DMC, select summaries will be tabulated by the following three applicable study time periods with respect to study part and study phase:

- Part 1, Phase A (1A)
- Part 2, Phase A (2A)
- Part 2, Phase B (2B)

Summaries will also be tabulated for Part 2 overall, to include data from all subjects with a planned treatment duration of 90 days. The following summaries will be tabulated as indicated above.

- Demographics
- Baseline characteristics
- Relevant protocol deviations
- Disposition
- Concomitant medications, including CYP3A4 inhibitor use
- Study drug exposure and compliance
- Bleeding events
- Adverse events, including overall AEs, SAEs, AEs leading to discontinuation, related AEs, and deaths
- Abnormal laboratory results, including renal biomarkers
- Abnormal ECG results
- Out of range vital signs

7.1.2 General Methods for Efficacy Analyses

Generalized Multiple Comparison Modelling (gMCP-Mod)

To demonstrate the dose-response relationship between BMS-986141 treatment (including placebo) and the primary endpoint, the primary analysis will be based on a generalized Multiple Comparisons and Modeling (gMCP-Mod) analysis[56]. This analysis tests for a dose-response relationship, allowing for uncertainty in the dose-response relationship through inclusion of contrasts from multiple 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 models.

The gMCP-Mod procedure extends the MCP-Mod methodology to non-continuous endpoints. This is accomplished by decoupling the dose-response model from the expected response through the use of an ANOVA style parameterization of the dose-response parameter. For the binary endpoint used in this study, a logistic regression of the event proportion at each dose level will be used, following adjustment for study time period (1A, 2A, 2B) via the inclusion of an additive covariate. After this first step, the mean parameter estimates from the logistic model and the corresponding covariance matrix, both of which are on the logit scale, will then be used during the rest of the gMCP-Mod procedure. Point estimates from the selected models will be displayed on the proportion scale in all statistical outputs.

Candidate Models and Multiple Testing Procedure

There are two candidate models that will be considered for the primary analysis. These are 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)[7].

The MCP-Mod procedure requires certain parameter estimates be pre-specified for the candidate models based on available information in order to derive optimum contrast coefficients for testing the null hypothesis: that a dose-response does not exist in any of the candidate models. It

is through testing this hypothesis that the model which best describes the dose-response relationship will be identified[8]. The parameters used to determine the contrast for testing will assume a placebo event rate of 14% and maximum risk reduction of 4.2%. For the Emax model, the required parameter estimates 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, these parameter estimates 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. These pre-specified parameter estimates will remain fixed through the contrast testing portion of the gMCP-Mod procedure in order to preserve the type I error.

The gMCP-Mod procedure for non-continuous endpoints diverges from the original MCP-Mod procedure in the calculation of the optimum contrast coefficients. The gMCP-Mod methods that will be used to calculate the optimum contrast coefficients require the pre-specified model parameters from above along with the covariance matrix from the logistic regression in the first step. In practice, since the covariance matrix in the first step is based on actual data, the optimum contrast coefficients are recalculated when the actual data become available. The parameter estimates for the candidate models, however, will remain fixed.

These optimal contrast coefficients follow the form given below, and will be recalculated as described using the DoseFinding package in R once the actual data are available.

$$c_m^{opt} \propto S^{-1}\left(\mu_m - \frac{\mu_m{}'S^{-1}1}{1'S^{-1}1}\right)$$

Where μ_m is the event rate on the logit scale based on the corresponding candidate model m (m=1, 2) at the specified dose levels, and S corresponds to the covariance matrix from the logistic regression on the actual data in the first step.

In order to demonstrate a dose-response relationship, the following global hypothesis will be tested:

H_0: $c_m^{opt}\mu \geq 0$ for all m $\in$ {1, 2}

H_1: $c_m^{opt}\mu < 0$ for at least one m $\in$ {1, 2}

where μ is the true event rate on the logit scale at the specified dose levels.

For each candidate model (m=1, 2), the contrast test statistic (z_m) is calculated as standardized linear combinations of the estimated event rate on the logit scale from the logistic regression using the optimal contrast coefficients associated with that candidate model.

A multiplicity-adjusted critical value will be determined from the joint multivariate normal distribution of the contrast test statistics at the overall one-sided alpha level of 0.15. If either test statistic that exceeds this critical value, a dose-response relationship will be demonstrated.

Modelling and Estimation

The model for estimation will be selected from among the two candidate models with a contrast test statistic that is greater than or equal to the multiplicity-adjusted critical value. If both

candidate models have such contrast test statistics, then both models will be employed using a weighted averaging technique based on their relative Bayesian Information Criteria (BIC), for the purposes of estimation. If neither candidate model has a contrast test statistic that is greater than or equal to the multiplicity-adjusted critical value, then the analysis will end, indicating that a dose-response relationship cannot be established.

In this manner, the point estimates for the means will be generated from the selected model as described in the efficacy analyses in Section 7.5.

7.2 Study Conduct

7.2.1 Accrual

The accrual pattern will be summarized per country, investigational site, and per month for all randomized subjects. Enrollment date, randomization date, first dosing date, country, investigational site will be presented in a by subject listing of accrual.

7.2.2 Relevant Protocol Deviations

Relevant deviations from the study protocol will be documented and accounted for in presenting the data summaries, listings and descriptive statistical analyses. Any changes from planned protocol-specified analyses will be defined in the SAP and reported in the CSR. The relevant protocol deviations are described in the table below.

Table 7.2.2-1: List of Relevant Protocol Deviations

Number	RPD Criteria
1	Subject randomized but not dosed
2	Error in treatment assignment (resulting in a subject receiving a treatment other than that assigned by the IVRS) during the first 28-day interval
3	Poor treatment compliance for either BMS-986141 or ASA (compliance less than 80% or more than 120%) during first 28-day interval
4	Randomized subjects with history of atrial fibrillation (AF) other than transient AF related to cardiac surgery at enrollment (per Exclusion Criteria 1a from the protocol)
5	Randomized subjects with unrecognized or misdiagnosed intracranial hemorrhage (ICH) as determined by the central reader based on the baseline study specific MRI (presence of type 1 or 2 parenchymal hematoma)
6	Randomized subjects who took no dose of ASA or dose of ASA not within limits designated by the protocol for ≥ 5 consecutive days in the first 28 days of the treatment period
7	Randomized subjects who took oral anticoagulants or prohibited antiplatelet therapy, other than study medication, for > 2 consecutive days during the first 28days of the treatment period
8	Randomized subjects that were treated with a strong CYP3A4 inhibitor for > 5 days during the first 28 days of the treatment period[a]

a: CYP3A4 inhibitors will be defined in a separate file maintained by the study team and will be classified as weak, moderate, or strong.

7.3 Study Population

All study population summaries will be presented by treatment and overall, as well as by study time period (1A, 2A, 2B) and for study part 2.

7.3.1 Subject Disposition

Subject disposition will be listed for all enrolled subjects. For subjects who are randomized, the subject's study part, gender, age, race, consent date, randomization date, first and last dosing date, reason for treatment discontinuation, off-study date, and reason for going off-study will be listed. For subjects who enroll, but are not treated, the subject's gender, age, race, consent date, and reason for not entering the treatment period will be listed.

Summary tables reflecting the number of subjects enrolled, randomized, and treated, reasons for not entering the treatment period, and number completing the study will be presented by treatment and study time period (1A, 2A, 2B), and for study part 2.

The number of subjects who do not complete treatment and also the number who do not complete the study, both overall and according to reasons for discontinuation, will also be summarized by treatment and study time period (1A, 2A, 2B), and for study part 2..

7.3.2 Demographic and Baseline Characteristics

The following baseline characteristics will be summarized by treatment group for all randomized subjects, overall, as well as by study time period (1A, 2A, 2B), and for study part 2. All baseline presentations will identify subjects with missing measurements.

- Age (descriptive statistics)
- Age category I, in years (< 65, ≥ 65)
- Age category II, in years (< 65, ≥ 65- < 75, ≥ 75)
- Gender (male, female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other pacific islander, Other)
- Ethnicity (Hispanic/Latino, Non Hispanic/Latino) for US subjects
- Geographical Region (North America, Europe, Asia / Pacific)
- Height, Weight, and BMI
- Acute Ischemic Stroke at Entry (Yes/No)
- National Institutes of Health Stroke Score (NIHSS) at Baseline
- High-risk Transient Ischemic Attack at Entry (Yes/No)
- Lacunar Infarct
- Diabetes mellitus (Yes/No)
- Cigarette use (Yes/No)
- Hypercholesterolemia (Yes/No)
- Hypertension (Yes/No)
- BMI Category (<18, 18-25, 25-30, 30-35, >35)

- Vital signs
- Time since onset of symptoms detected to randomization

7.3.3 Medical History

General medical history will be summarized by treatment and study time period (1A, 2A, 2B), and for study part 2.

7.4 Extent of Exposure

7.4.1 Administration of Study Therapy

The number of days on study medication received will be calculated as (date of first dose - date of last dose) + 1. The days on study medication will be summarized for all treated subjects by treatment and study time period (1A, 2A, 2B), and for study part 2 using descriptive statistics as well as categorically as given in the table below.

Table 7.4.1-1: Extent of Exposure Categories for Summarization

Part 1 Exposure Categories	Part 2 Exposure Categories
1 - 7 days	1 - 14 days
8 - 14 days	15 - 28 days
15 - 21 days	28 - 42 days
22 - 28 days	43 - 56 days
> 28 days	57 - 70 days
	71 - 84 days
	> 85 days

A by-subject listing of dosing of study medication and a listing of batch numbers will be also provided.

7.4.2 Study Therapy Compliance

Compliance with the protocol-specified study therapy will be summarized by treatment group for all treated subjects by treatment and study time period (1A, 2A, 2B), and for study part 2.

For randomized study therapy, the case report forms collect the number of doses taken per day. The kits dispensed for study treatment are expected to contain 4 pills per day during Phase A of the study while the high dose arm is closed. During Phase B, once the high-dose arm has opened, the number of pills dispensed to patients who are randomized from that point forward will be 2. Thus, compliance with randomized therapy dosing will be calculated as given below for each container of study therapy:

$$\%\ Compliance_{Randomized\ Therapy} = 100\ x\ \frac{Number\ of\ Tablets\ Taken\ per\ Day}{(\text{Phase A: } 4 \text{ or Phase B: } 2)}$$

Overall compliance will be calculated as the weighted average of the compliance for each container, weighted in proportion to the # of days each container was used.

Acetylsalicylic acid (ASA) is an adjuvant therapy that the protocol requires all subjects receive at a total daily dose that is between 75mg and 162mg. Overall compliance with ASA dosing will be calculated as given below:

$$\%\ Compliance_{ASA} = 100\ x\ \frac{Number\ of\ Days\ where\ protocol\ specified\ TDD\ was\ taken}{(Last\ Date\ Dosed - First\ Date\ Dosed) + 1}$$

In addition, compliance will also be summarized from the first dose date to the lesser of the last date dosed and 28 days after the first date dosed. The above calculations will be repeated using only data within this time period.

Summaries of compliance will be presented according to the general methods for continuous variables as well as categorically, according to the number and percentage of subjects with compliance in each of the following categories:

- < 80%
- ≥ 80% and ≤ 120%
- >120%

7.4.3 Modifications of Study Therapy

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 as specified in section 3.4.1 of the protocol.

7.4.4 Concomitant Medications

Concomitant medications, defined as medications other than study medications which are taken at any time on-treatment (ie, on or after the first day of study therapy and prior to the last dose of study therapy), will be coded using the WHO Drug Dictionary.

Concomitant medications will be summarized (subjects with any concomitant medication, subjects by medication class and generic term) for all treated subjects. Additionally, a separate, but similar summary of all concomitant medications that are moderate CYP3A4 inhibitors will be created.

7.5 Efficacy

Adjudicated events will be the basis for the primary and secondary analyses, including imaging assessments from the Imaging Adjudication Committee (IAC) and clinical assessments from the CEC. All efficacy analyses will be conducted on the Intent-To-Treat (ITT) population.

7.5.1 Primary Efficacy Analysis

Using the general methods for efficacy analyses described in 17, the observed incidence of the composite of symptomatic ischemic stroke by Day 28 and unrecognized brain infarction assessed

by MRI at Day 28 will be summarized by treatment using the fitted model from the gMCP-Mod procedure. It should be noted that the selected model from gMCP-Mod will actually be a model for the logit of the incidence rate. As a result, the point estimate will be converted and presented on the probability scale by treatment.

In addition, the raw proportion of incidence within each treatment group and its associated 95% Clopper-Pearson CI will be presented. The relative risk reduction between each BMS-986141 arm and placebo and the associated 95% CI will be presented as well. The form of the relative risk reduction between each treatment group and placebo is given below.

$$\frac{Incidence_{PBO} - Incidence_{TRT}}{Incidence_{PBO}} = 1 - \frac{Incidence_{TRT}}{Incidence_{PBO}}$$

7.5.1.1 Sensitivity Analyses

To assess the robustness of the primary efficacy analysis, additional sensitivity analyses will be carried out using the following approaches:

- Following the same procedure as the primary analysis, considering the All Evaluable Subjects population in place of the All Randomized Subjects population.
- A worst-case analysis that will repeat the primary analysis on the ITT population where any missing information that is consequential to the evaluation of the primary endpoint will be considered as an event.

7.5.1.2 Subgroup Analyses

All analyses described in this section will be performed on the ITT Population. Table 7.5.1.2-1 below shows the subgroups of interest for analyses of efficacy data. If the value of the grouping variable cannot be determined for a subject, the subject will be excluded from the corresponding subgroup analysis.

Table 7.5.1.2-1: Subgroups of Interest for Efficacy Assessments

Grouping Variable	Subgroups
Event at entry	Acute ischemic stroke Transient ischemic attack
Time since onset of symptoms detected to randomization	< 24 hours 24 - 48 hours
Lacunar infarct at entry	Yes No
Oxfordshire Community Stroke Project (OCSP) Subtype (only for stroke) at entry	Total Anterior Circulation Stroke (TAC) Lacunar Stroke (LAC) Partial Anterior Circulation Stroke (PAC) Posterior Circulation Stroke (POC)
ABCD2[a] Score (only for TIA) at entry	4-5 (moderate)

Table 7.5.1.2-1: Subgroups of Interest for Efficacy Assessments

Grouping Variable	Subgroups
Age	6-7 (high) < 65 years old ≥ 65 to < 75 years old ≥ 75 years old
Gender	Male Female
Race	White Black or African American Asian Other
Geographic Region	North America Europe Asia / Pacific

[a] age, blood pressure, clinical features, duration, diabetes

7.5.2 Secondary Efficacy Analyses

The same approach used in the primary analysis will be repeated on the secondary endpoints.

- 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 by Day 90
- 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

In addition, a sequential testing procedure will be used for the primary and MACE endpoints as described below.

1) If a dose-response relationship is established for the primary endpoint at the one-sided 0.15 level, then the primary analysis will be repeated at a one-sided alpha level of 0.025.
2) If this analysis at the one-sided 0.025 level also demonstrates a dose-response relationship, then the dose-response relationship for the MACE endpoint will be tested using a one-sided alpha level of 0.025.

Each of these sequential testing analyses will be performed. Their interpretation will be guided by the sequential testing procedure.

7.5.3 Other Efficacy Analyses

The primary analysis will be repeated for the composite endpoint of recurrent ischemic stroke or any adjudicated arterial thrombotic events up to 90 days. As well, the primary analysis will be repeated using each of its components, individually, as the response variable.

Additionally, the following exploratory analyses may be explored:

- [redacted]

7.6 Safety Analyses

Analysis of all safety data will be conducted on all treated subjects and will follow the BMS guideline of analysis of safety data[9]. Safety will be summarized for each parameter by treatment group, as well as for all subjects receiving BMS-986141. Summaries of the frequency of subjects experiencing certain events, such as adverse events, elevated labs or vital signs, or elevated ECGs, will be summarized by treatment and study time period (1A, 2A, 2B), and for study part 2.

The evaluation of safety is based on adjudicated bleeding events, clinical adverse events (AEs), vital signs, ECG results, and clinical laboratory results.

All AEs will be coded and grouped into Preferred Terms (PT) by System Organ Class (SOC), using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA). Summaries of AEs will use the version of MedDRA that is current at the time of database lock. All recorded adverse events will be listed and tabulated by SOC, PT, treatment and overall. Values for ECGs, vital signs, and clinical laboratory test results will be summarized by treatment. Abnormal results for ECG, vital signs and clinical laboratory tests that fall outside the pre-specified criteria will also be listed and summarized. In addition, ECG readings will be evaluated by the Investigator and abnormalities, if present, will be listed.

7.6.1 Major Bleeding and Clinically Relevant Non-Major Bleeding

The proportion of subjects with adjudicated bleeding events which occur on or after the first dose of study treatment and within 4 days after the last dose of study treatment will be summarized by treatment. Point estimates and 95% exact CIs for event rates of each of the below bleeding endpoints will be presented by treatment, together with point estimates and 95% exact CIs for the difference of event rates between each BMS-986141 arm and placebo. The following bleeding endpoints will be analyzed using these methods.

- The proportion of subjects with the composite of adjudicated major bleeding and CRNM bleeding
- The proportion of subjects with all reported bleeding
- The proportion of subjects with intracranial hemorrhage

All adjudicated bleeding events will be listed. In addition, the proportion of subjects with confirmed major bleeding or clinically relevant non-major bleeding events occurring during the treatment period will be summarized by treatment group for each of the following factors.

- Stroke severity (based on National Institutes of Health Stroke Scale NIHSS) at study entry
  - NIHSS Score of 0 (No stroke symptoms)
  - NIHSS Score of 1-4 (Minor stroke)
  - NIHSS Score of 5-15 (Moderate stroke)
- Lacunar infarct at study entry
  - Yes
  - No

7.6.2 Deaths

All reported deaths after a subject is enrolled (i.e., has signed the informed consent) will be listed separately by subject. Deaths will also be summarized by treatment group according to whether the death was determined to be CV-related, not CV related, or unknown, following adjudication.

7.6.3 Serious Adverse Events

All reported serious adverse events (SAEs) will be listed for all enrolled subjects. A summary of SAEs occurring from the day of the first dose of study drug through 30 days following the last dose of study drug will also be provided for all treated subjects by SOC and PT for each treatment group. A separate summary of SAEs related to study drug will also be provided.

7.6.4 Adverse Events

All AEs will be summarized by SOCs and PTs for each treatment group and also listed.

Adverse events which occur on or after the first dose of study treatment and within 4 days after the last dose of study treatment will be tabulated. Events will be assigned to the study treatment administered to the subject. The proportion of subjects having an adverse event will be calculated as the number of subjects experiencing the event, divided by the total number of subjects receiving study treatment.

A high-level summary will be presented by treatment group that counts subjects experiencing any of the following:

- At least one AE
- At least one related AE

- Deaths
- At least one SAE
- SAE leading to discontinuation of study drug
- AE leading to discontinuation of study drug

The above summary will also be presented by treatment and study time period (1A, 2A, 2B), and for study part 2.

All AE listings will indicate the unique subject identifier, age, gender, current treatment, the date of onset, the date of resolution, day of onset relative to the start of treatment, action taken, investigator's assessment of severity and relationship to study drug. Additional listings will be provided for adverse events leading to discontinuation, serious adverse events, adverse events leading to death, and adverse events without a recorded resolution. Summaries of adverse events will include adverse events, adverse events by intensity, adverse events leading to discontinuation, and adverse events by relationship.

All adverse events will be further summarized according to demographic factors for each of the categories given below:

- Age category I, in years (< 65, ≥ 65)
- Age category II, in years (< 65, ≥ 65- < 75, ≥ 75)
- Gender (male, female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other pacific islander, Other)

Where a subject has multiple adverse events within the level of summarization in a single analysis period, the subject will only be counted once at that level of summarization in the adverse event frequency tables.

When a subject has the same adverse event, based on preferred terminology, reported multiple times in a single analysis period, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- Relationship to study medication
- Intensity of event

When reporting adverse events by intensity, summary tables will be provided based on the most intense event during the analysis period - independent of relationship to study medication. Similarly, where a subject has multiple adverse events within the level of summarization in a single analysis period, the subject will only be counted once at that level of summarization in the adverse event frequency tables

7.6.5 Clinical Laboratory Evaluations

Summaries of laboratory test results and the corresponding change from baseline by treatment and nominal visit will be provided for those laboratory tests required at each study visit as given in Table 5.3.7-1 of the protocol.

The criteria used for classifying laboratory test results as markedly abnormal will be listed. These criteria are provided in an appendix to this SAP.

Laboratory results for subjects with any marked laboratory abnormality (scheduled and unscheduled) will be listed. This listing will include all observations for the specific laboratory test and subject, not only the marked laboratory abnormalities. The frequency of subjects with any marked laboratory abnormality will be presented by treatment and study time period (1A, 2A, 2B), and for study part 2.

In addition to the analysis of standard laboratory results, separate analyses will focus specifically on renal parameters. Renal biomarkers, including Cystatin-C, NGAL, and KIM-1 will be summarized according to the number and percentage of subjects in each treatment group with levels exceeding the upper limit of normal (ULN) at each study visit where labs are collected per protocol. Additionally, estimated Glomerular Filtration Rate (eGFR) using the Modification of Diet in Renal Disease formula (MDRD) will be summarized at each visit by the mean, standard deviation, range, and median.

Urinalysis results will also be summarized in the same manner as the laboratory test results.

7.6.6 Electrocardiograms

Summaries of ECG results and the corresponding change from baseline by treatment will be provided for the screening, Day 28, and end of treatment visits. The normality/abnormality of the ECG tracing, as determined by the investigator, will be summarized using frequency tables on the number of subjects who have a normal/abnormal ECG tracing at Day 28 and at Day 90 (Part 2 only). A listing of subjects with Investigator identified ECG abnormalities will also be provided.

7.6.7 Vital Signs

Vital sign measurements (systolic BP, diastolic BP, heart rate, respiratory rate and body temperature) and their respective changes from baseline will be summarized by nominal visit and treatment group.

The following criteria will be used to determine vital sign results that are out a range, where changes from baseline are based on matched postural positions:

Table 7.6.7-1: Out of Range Vital Signs Criteria

Vital Sign Measurement	Criteria
Heart Rate(bpm)	Value > 100 and change from baseline > 30, or Value < 55 and change from baseline < -15
Systolic BP(mmHg)	Value > 140 and change from baseline > 20, or Value < 90 and change from baseline < -20
Diastolic BP(mmHg)	Value > 90 and change from baseline > 10, or Value < 55 and change from baseline < -10

Subjects with vital signs out of range will also be listed.

7.6.8 Physical Examination Findings

All physical examination abnormal findings will be listed per subject and visit.

7.7 Pharmacokinetic Analyses

Analyses of pharmacokinetics will be conducted on the Pharmacokinetic Population. Pharmacokinetics of BMS-986141 and BMT-162856 will be summarized with descriptive statistics for Cmax, AUC(0-24), C(24) after first dose, and C(24) on Day 28.

As well, a population pharmacokinetic model will be developed to understand the pharmacokinetics of BMS-986141. The potential effect of covariates such as body weight, age, gender, race, renal function, liver function, and co-administration of other medicines on the pharmacokinetics of BMS-986141 will be explored in this analysis. Details of this analysis and its results will be reported in a separate document.

7.8 Biomarker Analyses

[redacted]

[redacted]

8 CONVENTIONS

Standard time windowing, imputation rules, and counting rules will be applied according to the GBS Requirements for Statistical Outputs[10]. Unless otherwise defined, baseline is defined as the last non-missing value prior to the first dose of study drug.

8.1 Decimal Places

The number of decimal places displayed in all listings will be determined by the number of decimal places in the raw data.

Unless otherwise specified, minimum and maximum will be reported to the precision as the data collected, one more decimal place for the mean and median, and two more decimal places for the standard deviation. The adjusted geometric mean, geometric mean ratio and the lower and upper limits of confidence interval will be displayed to three decimal places.

8.2 Pharmacokinetic Summaries

Handling of Non-Quantifiable Concentrations

For the summaries of plasma concentration-time data, concentrations that are less than the lower limit of quantification (LLOQ) should be displayed as "< LLOQ" in the listings and be treated as missing in summary tables and plots.

Summary statistics for PD-concentrations will be calculated by imputing values less than LLOQ as ½ * LLOQ.

8.3 Day Ranges for Analysis of Time Points

Subjects do not always adhere strictly to the visit schedule timing in the protocol. Therefore, the designation of visits for analysis of safety outcome measures during the treatment period will be based on the day of the start of study medication (Day 1). The day ranges for the analyses of laboratory, electrocardiogram (ECG) and vital sign measurements are defined in the following tables.

Table 8.3-1: Analysis Windows for Laboratory Parameters & Vital Signs (Part 1)

Visit Name	Lower Limit (Study Day)	Upper Limit (Study Day)
Day 1	1	1*
Day of Hospital Discharge	2	10
Day 28	11	N/A

* Pre-dose

Table 8.3-2: Analysis Windows for Laboratory Parameters & Vital Signs (Part 2)

Visit Name	Lower Limit (Study Day)	Upper Limit (Study Day)
Day 1	1	1*
Day of Hospital Discharge	2	10
Day 28	11	42
Day 56	43	68
Day 90	69	N/A

* Pre-dose

Table 8.3-3: Analysis Windows for ECG Results

Visit Name	Lower Limit (Study Day)	Upper Limit (Study Day)
Day 28	2	64[a]
Day 90[a]	65	N/A

a: Day 90 visit will only be conducted for subjects in Part 2 of the study. Subjects in Part 1 of the study will only have a Day 28 ECG scheduled after beginning treatment, with no applicable upper limit to the analysis window.

8.4 Multiple Measurements

Laboratory Measurements

For tabulations of changes from baseline or shift analyses, if multiple laboratory measurements are obtained within the same visit window, then the measurement obtained on the day closest to the target day for that visit window will be used; in the case of a tie, the measurement obtained on the earlier day will be used in the analyses.

For tabulations of incidence of marked abnormalities (e.g. ALT > 3xULN), if multiple laboratory measurements are obtained within the same visit window, then the worst measurement within the visit window will be used.

Vital Signs and ECGs

If multiple vital sign or ECG measurements are obtained within the same visit window, then the measurement obtained on the day closest to the target day for that visit window will be used; in the case of a tie, the measurement obtained on the earlier day will be used in the analyses.

9 CONTENT OF REPORTS

Statistical components for the clinical study report will be based on the content of this statistical analysis plan (SAP). Pharmacokinetic and exploratory biomarker results may be reported separately.

Details of the tables, listings, and figures to be prepared for the final CSR will be included in a study-specific Data Presentation Plan (DPP).

APPENDIX 1 MARKED ABNORMALITY CRITERIA FOR LABORATORY TEST RESULTS - CONVENTIONAL (US) UNITS

Clinical Laboratory Variables	Units	Low MA Criterion	High MA Criterion
HEMATOLOGY			
Hemoglobin	g/dL	> 2 g/dl decrease compared to pre-dose or value ≤ 8 g/dl	
Hematocrit	%	< 0.75 x pre-dose	
Erythrocytes	$x10^6$ cells/µL	< 0.75 x pre-dose	
Platelet Count	$x10^9$ cells/µL	< 100,000/mm^3 (or < 100x 10^9 cells/L)	
Leukocytes	$x10^3$ cells/µL	< 0.75 x LLN, or if pre-dose < LLN then use < 0.8 x pre-dose if pre-dose > ULN then use < LLN	> 1.25 x ULN, or if pre-dose < LLN then use > ULN if pre-dose > ULN then use > 1.2 x pre-dose
Neutrophils (absolute)	$x10^3$ cells/µL	< 1.0 x 10^3 cells/µL	
Neutrophils + Bands (absolute)	$x10^3$ cells/µL	< 1.0 x 10^3 cells/µL	
Eosinophils (absolute)	$x10^3$ cells/µL		> 0.750 x 10^3 cells/µL
Basophils (absolute)	$x10^3$ cells/µL		> 400/mm^3 (or > 0.4 x 10^3 cells/µL)
Monocytes (absolute)	$x10^3$ cells/µL		> 2000/mm^3 (or > 2 x 10^3 cells/µL)
Lymphocytes (absolute)	$x10^3$ cells/µL	< 0.750 x 10^3 cells/µL	> 7.50 x 10^3 cells/µL
LIVER/KIDNEY			
Alkaline Phosphatase	U/L		> 2 x ULN
Aspartate Aminotransferase	U/L		> 3 x ULN
Alanine Aminotransferase	U/L		> 3 x ULN
Bilirubin, Total	mg/dL		> 2 x ULN
Bilirubin, Direct	mg/dL		> 1.5 x ULN
Blood Urea Nitrogen	mg/dL		> 2 x ULN
Creatinine	mg/dL		> 1.5 x ULN
ELECTROLYTES			

APPENDIX 1 MARKED ABNORMALITY CRITERIA FOR LABORATORY TEST RESULTS - CONVENTIONAL (US) UNITS

Clinical Laboratory Variables	Units	Low MA Criterion	High MA Criterion
Sodium, Serum	mEq/L	< 0.95 x LLN, or if pre-dose < LLN then use < 0.95 x pre-dose if pre-dose > ULN then use < LLN	> 1.05 x ULN, or if pre-dose < LLN then use > ULN if pre-dose > ULN then use > 1.05 x pre-dose
Potassium, Serum	mEq/L	< 0.9 x LLN, or if pre-dose < LLN then use < 0.9 x pre-dose if pre-dose > ULN then use < LLN	> 1.1 x ULN, or if pre-dose < LLN then use > ULN if pre-dose > ULN then use > 1.1 x pre-dose
Chloride, Serum	mEq/L	< 0.9 x LLN, or if pre-dose < LLN then use < 0.9 x pre-dose if pre-dose > ULN then use < LLN	> 1.1 x ULN, or if pre-dose < LLN then use > ULN if pre-dose > ULN then use > 1.1 x pre-dose
Calcium, Total	mg/dL	< 0.8 x LLN, or if pre-dose < LLN then use < 0.75 x pre-dose if pre-dose > ULN then use < LLN	> 1.2 x ULN, or if pre-dose < LLN then use > ULN if pre-dose > ULN then use > 1.25 x pre-dose
Bicarbonate	mEq/L	< 0.75 x LLN, or if pre-dose < LLN then use < 0.75 x pre-dose if pre-dose > ULN then use < LLN	> 1.25 x ULN, or if pre-dose < LLN then use > ULN if pre-dose > ULN then use > 1.25 x pre-dose
Phosphorus	mg/dL	If pre-dose = missing then use < 0.85 x LLN If LLN ≤ pre-dose ≤ ULN then use < 0.85 x LLN If pre-dose < LLN then use < 0.85 x pre-dose If pre-dose > ULN then use < LLN	If pre-dose = missing then use > 1.25 x ULN If LLN ≤ pre-dose ≤ ULN then use > 1.25 x ULN If pre-dose > ULN then use > 1.25 x ULN If pre-dose < LLN then use > ULN
OTHER CHEMISTRY			
Lactate Dehydrogenase (LDH)	U/L		If pre-dose = missing then use > 1.25 x ULN If pre-dose ≤ ULN then use > 1.25 x ULN If pre-dose > ULN then use > 1. 5 x pre-dose
Total Protein	g/dL	< 0.9 x LLN, or if pre-dose < LLN then use 0.9 x pre-dose if pre-dose > ULN then use < LLN	> 1.1 x ULN, or if pre-dose < LLN then use > ULN if pre-dose > ULN then use 1.1 x pre-dose
Albumin	g/dL	If pre-dose = missing then use < 0.9 x LLN	

APPENDIX 1 MARKED ABNORMALITY CRITERIA FOR LABORATORY TEST RESULTS - CONVENTIONAL (US) UNITS

Clinical Laboratory Variables	Units	Low MA Criterion	High MA Criterion
Glucose, Serum Fasting	mg/dL	if pre-dose ≥ LLN then use < 0.9 x LLN If pre-dose < LLN then use < 0.9 x pre-dose < 0.8 x LLN, or if pre-dose < LLN then use < 0.8 x pre-dose if pre-dose > ULN then use < LLN	> 1.5 x ULN, or if pre-dose < LLN then use > ULN if pre-dose > ULN then use > 2.0 x pre-dose
Uric Acid	mg/dL		> 1.5 x ULN, or if pre-dose > ULN then use > 2 x pre-dose
URINALYSIS			
Glucose Urine	N/A		if missing pre-dose then use≥ 2, or if value ≥ 4, or if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4
Protein, Urine	N/A		If missing pre-dose then use ≥ 2, or if value ≥ 4, or if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4
Blood, Urine	N/A		If missing pre-dose then use ≥ 2, or if value ≥ 4, or if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4
Leukocyte Esterase, Urine	N/A		If missing pre-dose then use ≥ 2, or if value ≥ 4, or if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4
RBC, Urine	hpf		If missing pre-dose then use ≥ 2, or if value ≥ 4, or

APPENDIX 1 MARKED ABNORMALITY CRITERIA FOR LABORATORY TEST RESULTS - CONVENTIONAL (US) UNITS

Clinical Laboratory Variables	Units	Low MA Criterion	High MA Criterion
			if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4
WBC, Urine	hpf		If missing pre-dose then use ≥ 2, or if value ≥ 4, or if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4

APPENDIX 2 MARKED ABNORMALITY CRITERIA FOR LABORATORY TEST RESULTS -- SI UNITS

Clinical Laboratory Variables	Units	Low MA Criterion	High MA Criterion
HEMATOLOGY			
Hemoglobin	g/L	> 20 g/l decrease compared to pre-dose or value ≤ g/l	
Hematocrit	Vol	< 0.75 pre-dose	
Erythrocytes	$x10^{12}$ c/L	< 0.75 pre-dose	
Platelet Count	$x10^9$ cells/L	< 100 $x10^9$ cells/L	
Leukocytes	$x10^9$ cells/L	< 0.75 x LLN, or if pre-dose < LLN then use < 0.8 x pre-dose if pre-dose > ULN then use < LLN	> 1.25 x ULN, or if pre-dose < LLN then use > ULN if pre-dose > ULN then use > 1.2 x pre-dose
Neutrophils (absolute)	$x10^9$ cells/L	< 1.0 x 10^9 cells/L	
Neutrophils + Bands (absolute)	$x10^9$ cells/L	< 1.0 x 10^9 cells/L	
Eosinophils (absolute)	$x10^9$ cells/L		> 0.750 x 10^9 cells/L
Basophils (absolute)	$x10^9$ cells/L		> 0.4 x 10^9 cells/L
Monocytes (absolute)	$x10^9$ cells/L		> 2 x 10^9 cells/L
Lymphocytes (absolute)	$x10^9$ cells/L	< 0.750 x 10^3 cells/µL	> 7.50 x 10^9 cells/L
LIVER/KIDNEY			
Alkaline Phosphatase	U/L		> 2 x ULN
Aspartate Aminotransferase	U/L		> 3 x ULN
Alanine Aminotransferase	U/L		> 3 x ULN
Bilirubin, Total	umol/L		> 2 x ULN
Bilirubin, Direct	umol/L		> 1.5 x ULN
Blood Urea Nitrogen	umol/L		> 2 x ULN
Creatinine	umol/L		> 1.5 x ULN
ELECTROLYTES			
Sodium, Serum	mmol/L	< 0.95 x LLN, or if pre-dose < LLN then use < 0.95 x pre-dose if pre-dose > ULN then use < LLN	> 1.05 x ULN, or if pre-dose < LLN then use > ULN if pre-dose > ULN then use > 1.05 x pre-dose

APPENDIX 2 MARKED ABNORMALITY CRITERIA FOR LABORATORY TEST RESULTS -- SI UNITS

Clinical Laboratory Variables	Units	Low MA Criterion	High MA Criterion
Potassium, Serum	mmol/L	< 0.9 x LLN, or if pre-dose < LLN then use < 0.9 x pre-dose if pre-dose > ULN then use < LLN	> 1.1 x ULN, or if pre-dose < LLN then use > ULN if pre-dose > ULN then use > 1.1 x pre-dose
Chloride, Serum	mmol/L	< 0.9 x LLN, or if pre-dose < LLN then use < 0.9 x pre-dose if pre-dose > ULN then use < LLN	> 1.1 x ULN, or if pre-dose < LLN then use > ULN if pre-dose > ULN then use > 1.1 x pre-dose
Calcium, Total	mmol/L	< 0.8 x LLN, or if pre-dose < LLN then use < 0.75 x pre-dose if pre-dose > ULN then use < LLN	> 1.2 x ULN, or if pre-dose < LLN then use > ULN if pre-dose > ULN then use > 1.25 x pre-dose
Bicarbonate	mmol/L	< 0.75 x LLN, or if pre-dose < LLN then use < 0.75 x pre-dose if pre-dose > ULN then use < LLN	> 1.25 x ULN, or if pre-dose < LLN then use > ULN if pre-dose > ULN then use > 1.25 x pre-dose
Phosphorus	mmol/L	If pre-dose = missing then use < 0.85 x LLN If LLN ≤ pre-dose ≤ ULN then use < 0.85 x LLN If pre-dose < LLN then use < 0.85 x pre-dose If pre-dose > ULN then use < LLN	If pre-dose = missing then use > 1.25 x ULN If LLN ≤ pre-dose ≤ ULN then use > 1.25 x ULN If pre-dose > ULN then use > 1.25 x ULN If pre-dose < LLN then use > ULN
OTHER CHEMISTRY			
Lactate Dehydrogenase (LDH)	U/L		If pre-dose = missing then use > 1.25 x ULN If pre-dose ≤ ULN then use > 1.25 x ULN If pre-dose > ULN then use > 1. 5 x pre-dose
Total Protein	g/L	< 0.9 x LLN, or if pre-dose < LLN then use 0.9 x pre-dose if pre-dose > ULN then use < LLN	> 1.1 x ULN, or if pre-dose < LLN then use > ULN if pre-dose > ULN then use 1.1 x pre-dose
Albumin	g/L	If pre-dose = missing then use	

APPENDIX 2 MARKED ABNORMALITY CRITERIA FOR LABORATORY TEST RESULTS -- SI UNITS

Clinical Laboratory Variables	Units	Low MA Criterion	High MA Criterion
		< 0.9 x LLN if pre-dose ≥ LLN then use < 0.9 x LLN If pre-dose < LLN then use < 0.9 x pre-dose	
Glucose, Serum Fasting	mmol/L	< 0.8 x LLN, or if pre-dose < LLN then use < 0.8 x pre-dose if pre-dose > ULN then use < LLN	> 1.5 x ULN, or if pre-dose < LLN then use > ULN if pre-dose > ULN then use > 2.0 x pre-dose
Uric Acid	mmol/L		> 1.5 x ULN, or if pre-dose > ULN then use > 2 x pre-dose
URINALYSIS			
Glucose Urine	N/A		If missing pre-dose then use ≥ 2, or if value ≥ 4, or if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4
Protein, Urine	N/A		f missing pre-dose then use ≥ 2, or if value ≥ 4, or if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4
Blood, Urine	N/A		If missing pre-dose then use ≥ 2, or if value ≥ 4, or if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4
Leukocyte Esterase, Urine	N/A		If missing pre-dose then use ≥ 2, or if value ≥ 4, or if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4

APPENDIX 2 MARKED ABNORMALITY CRITERIA FOR LABORATORY TEST RESULTS -- SI UNITS

Clinical Laboratory Variables	Units	Low MA Criterion	High MA Criterion
RBC, Urine	hpf		If missing pre-dose then use ≥ 2, or if value ≥ 4, or if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4
WBC, Urine	hpf		If missing pre-dose then use ≥ 2, or if value ≥ 4, or if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4

10 REFERENCES

[1] Geeganage, C. M., et al. Dual or mono antiplatelet therapy for patients with acute ischemicstroke or transient ischemic attack: a systematic review and meta-analysis of randomized controlled trials. Stroke, 2012; 43: p. 1058-1066.

[2] International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19,435 patients with acute ischemic stroke. The Lancet, 1997; 349: p. 1569-1581.

[3] Sandercock PAG, Counsell C, TsengMC, Cecconi E.Oral antiplatelet therapy for acute ischaemic stroke. Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD000029. DOI: 10.1002/14651858.CD000029.pub3.

[4] Bornkamp B, Pinheiro J, Bretz F. DoseFinding: planning and analyzing dose finding experiments. R package, http://www.cran.rproject. org/web/packages/DoseFinding/.

[5] Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics 2005; 61:738–748.

[6] Pinheiro J, Bornkamp B, Glimm E, Bretz F. Model-based dose finding under model uncertainty using general parametric models. Statistics in Medicine 2014; 33:1646-1661.

[7] Bornkamp B, Pinheiro J, Bretz F. DoseFinding: planning and analyzing dose finding experiments. R package, http://www.cran.r-project.org/web/packages/DoseFinding/.

[8] Bornkamp B, Pinheiro J, Bretz F. MCPMod: An R Package for the Design and Analysis of Dose-Finding Studies. Journal of Statistical Software, February 2009; Volume 29, Issue 7.

[9] CT SOP 109, Analysis of Safety Data. Bristol-Myers Squibb Research and Development, September 2010.

[10] Bristol-Myers-Squibb Global Biometrics Sciences General Requirements for Statistical Outputs, Revision 1.8.5, 06-Nov-2013.