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Clinical Protocol CV010010

A Study to Assess Safety and Tolerability of Single Oral Doses of BMS-986177 in Patients with ESRD treated with chronic hemodialysis

Revised Protocol Number: 03

Medical Monitor/Study Director
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to partners to which BMS has transferred obligations, e.g., a Contract Research Organization (CRO).

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.

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1 SYNOPSIS

N/A

2. SCHEDULE OF ACTIVITIES

Table 2.-1: Procedural Outline Screening

Procedure	Screening Visit (up to 28 days prior to First Dose)[a]	Notes
Eligibility Assessments		
Informed Consent	x	A participant is considered enrolled only when a protocol specific informed consent is signed.
Inclusion/Exclusion Criteria	x	
Medical History	x	Include any toxicities or allergy related to previous treatments.
Concomitant Medications	x	
Safety Assessments		
Physical Examination (PE)	x	If the screening PE is performed within 24 hours prior to dosing on Day 1 then a single exam may count as both the screening and pre-dose evaluation.
Physical Measurements	x	Includes height, weight, and BMI.
Vital Signs	x	Includes body temperature, respiratory rate, and seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
Electrocardiogram (ECGs)	x	ECGs should be recorded after the participant has been supine for at least 5 minutes.
Laboratory Tests		
Drug Screen (urine or saliva)	x	
Alcohol Screen	x	Breathalyzer
Clinical Labs	x	Chemistry, CBC, Coagulation and urine dipstick for blood (if participant is able to produce urine).
Serology	x	HIV
Pregnancy test	x	WOCBP only. See Section 9.4.4.
Stool sample for occult blood	x	Subjects may bring sample to the unit on or prior to D1.
Adverse Event Reporting		
Monitor for Serious Adverse Events	x	All SAEs must be collected from the date of participant's written consent until 30 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.

[a] Screening and Day -1 to -3 activities can be combined if performed on the same day

Table 2.-2: Procedural Outline Treatment

Procedure	D -1 to -3	D 1	D5	D8	D12	D13 to D15 /Study Discharge[a]	Notes
Safety Assessments							
Physical Examination (PE)	x						
Targeted PE		x	x	x	x	x	Targeted physical based on subject complaint.
Concomitant Medications	x	x	x	x	x	x	
Physical Measurements	x	x	x	x	x		Weight only. Collect prior to Day 1 visit and collect pre and post dialysis (SoC can be used).
Vital Signs	x	x	x	x	x	x	Includes body temperature, respiratory rate, seated blood pressure (BP), and heart rate (HR) on Day -1 to -3 and for those that discontinue prematurely. BP and HR (pre-dose & 3h post HD for all treatments on Days 1, 5, 8, and 12, at 24h post-dose only when BMS-986177 is administered). BP and HR should be measured after the participant has been resting quietly for at least 5 minutes.
Electrocardiogram (ECGs)	x	x	x	x	x		ECGs should be performed prior to Day 1 and conducted 3-6 hours post dialysis. (See note in screening procedures, Section 2)
Laboratory Tests	x	x	x	x	x	x	Labs should be obtained prior to Day 1 and obtained 3-6 h post dialysis. (See note in screening procedures,Section 9.4.4.)
Stool, occult blood	x	x	x	x	x		Anytime 2-20 h post-HD. Can bring sample to next HD session.
Pregnancy Test	x					x	WOCBP only. See Section 9.4.4.
Urine dipstick		x	x	x	x		For blood if urine is produced by the participant.

Table 2.-2: Procedural Outline Treatment

Procedure	D -1 to -3	D 1	D5	D8	D12	D13 to D15 /Study Discharge[a]	Notes
							Obtain Pre-dose if possible; anytime up to 2- 20 h post HD if possible.
Drug Test (urine or saliva or plasma)	x						
Alcohol screen		x	x	x	x		Breathalyzer; Pre-dose
Adverse Event Reporting							
Monitor for Non-Serious Adverse Events		x	x	x	x	x	AE collection to begin 3 hours prior to dialysis start on Day 1 regardless of study drug administered
Monitor for Serious Adverse Events	x	x	x	x	x	x	See note in screening procedures.
Pharmacokinetic (PK) Assessments							
Serial Blood PK Sampling		x	x	x	x		See Section 9.5. PK only being collected on days when BMS-986177 is administered depending on randomization.
Single PK Sampling		Obtained 24-72 hours after each dose					
Pharmacodynamic (PD) Assessments							
Serial Blood PD Sampling		x	x	x	x		See Section 9.6 and Table 9.6-1 (for BMS-986177 and enoxaparin) and Table 9.6-2 (for UFH).
Single PD Sampling		Obtained 24-72 hours after each dose of BMS-986177 only.					Only after BMS-986177 dosing. See Section 9.6 and Table 9.6-1.
Biomarker Assessments							
D-dimer, F1,2 and exploratory plasma sample		x	x	x	x		See Section 9.8 and Table 9.8-1 and Table 9.8-2.

Table 2.-2: Procedural Outline Treatment

Procedure	D -1 to -3	D 1	D5	D8	D12	D13 to D15 /Study Discharge[a]	Notes
FXI antigen		x					See Section 9.8 and Table 9.8-1 and Table 9.8-2.
Clotting assessment for dialysis filter, drip chamber; dialysis circuit pressure; number and volume of saline flushes; Kt/V, Time to hemostasis at puncture site		x	x	x	x		See Section 9.8 and Table 9.8-1 and Table 9.8-2. Clotting Assessment to be conducted by a blinded staff member.
Retain dialysis filter		x	x	x	x		See Section 9.8.
Whole Blood Collection for Analysis of DNA Variants in ADME-related Genes and thrombosis and hemostasis related genes	x						See Section 9.7. Only one sample required per subject for the study. Maybe obtained any time on or after randomization
Additional Research Sampling		x	x	x	x (24-72 h post dose D12)		Residual samples from biomarkers and PD blood. See Section 9.8.1.
Clinical Drug Supplies							
Randomize	x						Visit can be conducted with scheduled HD session.
Study Drug Administration		x	x	x	x		Administration of study drugs (i.e., BMS-986177, enoxaparin, and UFH) will be depending on the randomized sequence the subject is assigned to.

[a] Visit can be performed between D13-15 based on last PK sample obtained between 24-72 hours post D12 dose. End of study procedures should be performed for subjects that discontinue prematurely.

In the event of multiple procedures are required at a single time point, the following is a list of procedures from highest priority to low:

- Safety
- Pharmacokinetic Sampling
- Pharmacodynamic Sampling
- Biomarker sampling

[redacted]

3.1 Study Rationale

Patients with end-stage renal disease (ESRD) in chronic treatment with hemodialysis (HD), are administered anticoagulant agents before and during the HD sessions to prevent clotting of the extracorporeal circuit. Clot formation in the hemodialysis circuit can reduce the efficiency of the procedure and, in the most severe cases, lead to complete occlusion of the lines or the hemodialytic filter with the consequent interruption of the HD and blood loss for the patient. Guidelines for clotting prevention recommend unfractionated heparin (UFH) or low-molecular-

weight heparin such as enoxaparin, is administered during the HD session. However, UFH and LMWH can potentially increase the hemorrhagic risk in patients with ESRD who frequently exhibit a uraemia-associated platelet dysfunction. Furthermore, some patients treated with heparins develop anti-heparin antibodies causing an autoimmune disorder called heparin-induced thrombocytopenia (HIT) that prevents further use of heparin. In this regard, FXIa inhibition might represent an alternative and safer anticoagulant option in patients undergoing HD in whom heparin administration is not indicated. Anti-coagulant agents are utilized in clinical practice to reduce the incidence of thrombotic agents in several conditions, and although effective in preventing thrombus formation, they are also associated with dose-related bleeding complications. Observations from patients with genetic deficit of FXI and from clinical and preclinical studies that investigated this mechanism of action suggest that inhibition of FXIa may be safer in terms of bleeding risk compared to other anti-coagulants. If this is confirmed, BMS-986177 may in the future be also used to prevent or treat thrombotic events. Thus, this study will also provide relevant information on the anticoagulant activity of BMS-986177 compared to two different comparators (UFH and enoxaparin) that are routinely used in several thrombotic conditions.

Research hypothesis

The purpose of this study is to evaluate the safety profile, tolerability, and pharmacokinetics of single oral doses of BMS-986177 in ESRD patients undergoing chronic stable hemodialysis treatment. Although there is no primary research hypothesis to be formally tested, it is expected that administration of BMS-986177 will prolong the plasma activated partial thromboplastin time (aPTT), reduce plasma Factor XI clotting activity, and have no effect on the prothrombin time and international normalized ratio (PT and INR).

It is expected that the administration of BMS-986177 will prevent clot formation in the extracorporeal HD circuit, hence clotting in the HD filter, lines, and drip chambers will be assessed, additional clotting-related pharmacodynamic (PD) endpoints will be also explored.

clinically apparent bleeding or bruising; puncture sites will be closely monitored and patients will be discharged from the study unit only once hemostasis at those sites has been reached. Additionally, phlebotomy may cause blood clots, discomfort, and/or inflammation at the respective sites.

Patients' progression in the study will depend on the clinical safety profile, including reported AEs, findings from physical examinations, clinical laboratory results, vital signs, and ECGs of all previous arms to and including the preceding dose.

A study of pharmacokinetic of BMS-986177 in patients with severe renal impairment undergoing hemodialysis (CV010-012) is ongoing. Data from the first 4 patients of CV010-012 have been analyzed to characterize PK and dialytic clearance in this patient population. The results from this modeling and simulation guided final dose selection for this study to attain target concentrations and avoid exceeding target exposures (see Section 5.5 Justification for Dose).

Reproductive toxicology studies have been performed for BMS-986177 and support, women of child-bearing potential (WOCBP) to be included in the study (For additional information refer to the Investigator's Brochure). WOCBP undergoing dialysis receive UFH or LMWH. All WOCBP will be monitored for pregnancy.

In summary, the overall safety profile of BMS-986177 in non-clinical and clinical studies supports further evaluation of the safety, tolerability, PK profile, and pharmacodynamic (PD) responses in ESRD patients undergoing HD. While the adverse effects observed in nonclinical studies at high multiple of exposure were not observed in healthy volunteers, these signals (LFTs) will be monitored in the setting of the current clinical study. All patients will be informed of the potential risks prior to enrollment in the study

4. OBJECTIVES AND ENDPOINTS

Table 4.-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess safety and tolerability of single oral doses of BMS-986177 in patients with end-stage renal disease on chronic hemodialysis treatment.	• AEs, clinical laboratory values, vital signs, ECGs.
Secondary	
• To characterize the pharmacokinetic profile of BMS-986177 in a hemodialysis population, and determine the extent of BMS-986177 on dialytic removal.	• Cmax, AUC, dialytic clearance.
[redacted]	[redacted]

Table 4.-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	[redacted]

5. STUDY DESIGN

5.1 Overall Design

This study is a multicenter, cross-over, randomized, open-label trial with blinded endpoint assessment investigating safety and tolerability of single oral doses of BMS-986177 in patients with ESRD undergoing chronic stable HD three times per week. Secondary objectives are to assess BMS-986177 pharmacokinetics and hemodialysis success defined as completion of hemodialysis without premature interruption of the procedure due to complete clotting of the dialytic circuit and/or filter.

Study treatments will be administered on the first and last HD day of the week (either Monday and Friday, or Tuesday and Saturday, depending on the patients HD schedule), for a total of 4 treatment days (2 doses of BMS-986177, 1 dose of UFH, 1 dose of Enoxaparin).

The 2nd HD day of the week is not a study treatment day; on that day, study patients will undergo dialysis with standard of care, as per their schedule, and no study activities will be performed on those days.

Screening for inclusion in the study will be performed up to 28 days before the first study visit. After screening and meeting eligibility as per inclusion and exclusion criteria, patients will be randomized to 1 of following 4 sequences that will be conducted in parallel.

Sequence No.	Period			
	1	2	3	4
1	UFH	BMS dose 1 (BMS-986177 100 mg)	BMS dose 2 (BMS-986177 300 mg)	Enoxaparin
2	BMS dose 1 (BMS-986177 100 mg)	Enoxaparin	UFH	BMS dose 2 (BMS-986177 300 mg)
3	BMS dose 2 (BMS-986177 300 mg)	UFH	Enoxaparin	BMS dose 1 (BMS-986177 100 mg)
4	Enoxaparin	BMS dose 2 (BMS-986177 300 mg)	BMS dose 1 (BMS-986177 100 mg)	UFH

Note: Per amendment/revised protocol 01, the BMS-986177 doses will be 100 mg (BMS dose 1) and 300 mg (BMS dose 2).

Study patients will be admitted to the study facility the same day of HD treatment day or the night before. Assessment of vital signs and clinical biochemistry will be performed pre-dose.

Study treatments will be administered:

- BMS-986177: one single oral dose 3 hours prior beginning the HD session
- UFH: I.V. infusion to start within 10 minutes prior beginning the HD session. The dosage and duration of UFH use are at the discretion of the physicians and are per their institutional practice.
- Enoxaparin: one single dose (40 mg) by subcutaneous injection 3 hours prior beginning the HD session

The HD session will last approximately 4 hours. However, the duration could range from 3 to 4 hours but should be consistent on the days when study drug is administered. After the HD, patients will remain in the study facility for at least:

- Approximately 3 hours post-HD on UFH and Enoxaparin treatment days
- Approximately 24 hours post-dose on BMS-986177 days

Site staff members blinded to treatment will perform an assessment of clot formation according to criteria set forth in the Clot Formation Assessment Manual which will be provided to the site in a separate document.

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. Participants will be closely monitored for adverse events throughout the study. Blood samples will be collected for up to 72 hours after study drug administration for pharmacokinetic (PK) analysis and pharmacodynamic (PD) analysis. Approximately 365 mL of blood will be drawn from each participant during the study.

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

Figure 5.1-1: Study Design Schematic

		Week 1							Week 2						
Days	D-21 to D-1	D1*	D2	D3	D4	D5‡	D6	D7	D8*	D9	D10	D11	D12‡	D13 to D15	
HD days		1st HD		2nd HD		3rd HD			1st HD		2nd HD		3rd HD		
Study activity	S - E - R	Tx				Tx			Tx				Tx	D	

HD = Hemodialysis session. S= Screening. E = Enrollment. R = Randomization. Tx = Study treatment day (BMS-986177 dose 1 or dose 2, or unfractionated heparin, or enoxaparin). D = Study discharge.

* D1 and D8 can be Monday or Tuesday depending on the patient's dialysis schedule.

‡ D5 and D12 can be Friday or Saturday depending on the patient's dialysis schedule.

Note: Per amendment/revised protocol 01, the BMS-986177 doses will be 100 mg (BMS dose 1) and 300 mg (BMS dose 2).

5.1.1 Data Monitoring Committee and Other External Committees

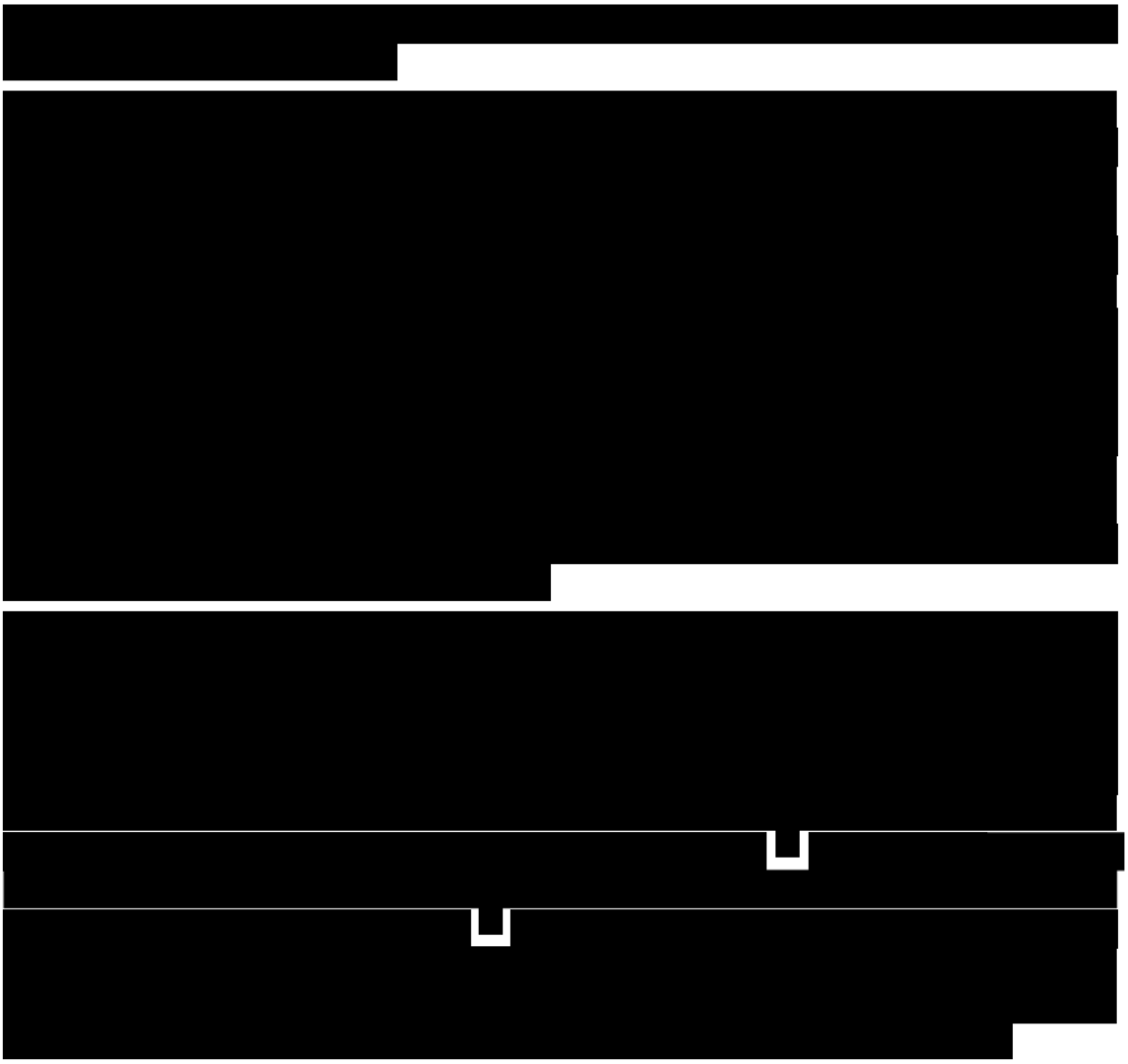
Not Applicable

5.2 Number of Participants

Target sample size is 32 participants to achieve 24 participants who completed the 4 study treatments.

5.3 End of Study Definition

The start of the trial is defined as the first visit for first participant screened. End of trial is defined as the last visit or scheduled procedure shown in the Schedule of Activities for the last participant. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected.



6. STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) The signed informed consent form.

2) Type of Participant and Target Disease Characteristics

a) Subjects with ESRD treated with hemodialysis prescribed 3 times a week for at least 3 months prior enrollment. For at least 2 weeks prior to study drug administration, participants should undergo all 3 hemodialysis sessions per week.

b) Subjects with severe renal impairment may include those with a variety of underlying stable renal disease such as nephrosclerosis and chronic glomerulonephritis.

3) Age and Reproductive Status

a) Males and Females, ages 18 or age of majority to 75 years, inclusive
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 treatment.
c) Women must not be breastfeeding
d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of the study plus 5 half-lives of study treatment BMS-986177 (2 days) plus 30 days (duration of ovulatory cycle) for a total of 32 days post-treatment completion.
e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatment(s) BMS-986177 plus 5 half-lives of the study treatment (2 days) plus 90 days (duration of sperm turnover) for a total of 92 days post-treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.
    i) With amendment/revised protocol 02, males who are sexually active with WOCBP must agree to follow instructions for methods of contraception (Appendix 4) for the duration of treatment with BMS-996177 plus 5 half-lives of the study treatment (2 days) for a total of 2 days post-treatment completion.
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.

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

6.2 Exclusion Criteria

1) Medical Conditions

a) Subjects receiving dialysis through central venous catheters. After amendment/revised protocol 01, this exclusion criteria will not be applicable and will not be needed for eligibility.
b) History of uncontrolled or unstable cardiovascular, respiratory, hepatic, gastrointestinal, endocrine, hematopoietic, psychiatric and/or neurological disease in the past 3 months
c) Evidence or history of coagulopathy, prolonged or unexplained clinically significant bleeding, or frequent unexplained bruising.
d) Current or recent (within 3 months of study drug administration) gastrointestinal disease or surgery, which by the judgment of the Investigator, may increase a subject's risk of gastrointestinal bleeding or interfere with absorption of study drug (eg, peptic or gastric ulcer disease, severe gastritis, history of gastrointestinal surgery with the exception of history of cholecystectomy).

e) Any condition requiring chronic systemic anticoagulation such as, but not limited to, atrial fibrillation, mechanical prosthetic valve, deep venous thrombosis, or pulmonary embolism

f) Not considered by the study principal investigator to be candidates for oral anticoagulation (for example, history of intracranial hemorrhage, active bleeding, recent gastrointestinal bleed or retroperitoneal bleed, severe hepatic impairment)

g) Any major surgery within 12 weeks of study drug administration

h) History of significant head injury within the last 2 years, including subjects with base of skull fractures

i) Donation of blood to a blood bank within 4 weeks of study drug administration (within 2 weeks for plasma only)

j) Blood transfusion within 2 weeks of study drug administration

k) Inability to tolerate oral medication

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

m) Smoking more than 10 cigarettes per day

n) Recent (within 6 months of study drug administration) drug or alcohol abuse as defined in DSM IV, Diagnostic Criteria for Drug and Alcohol Abuse (Appendix 6)

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

2) Prior/Concomitant Therapy

a) Chronic therapy with aspirin, dipyridamole, or P2Y12 antagonists (for example clopidogrel, prasugrel, or ticagrelor). Prior aspirin use is allowed after a washout period of at least 1 week before dosing.

b) Inability to comply with prohibited/restricted treatments as listed in Section 7.7

3) Physical and Laboratory Test Findings

a) Evidence of organ dysfunction or any clinically significant deviation in physical examination, vital signs, ECG or clinical laboratory determinations beyond what is consistent with their degree of renal dysfunction and other underlying conditions as determined by medical history, physical examination, ECG, and clinical laboratory determinations.

b) Subjects with macro-hematuria and/or fecal occult blood detected during screening, baseline, or documented during other recent medical assessment, unless deemed not clinically significant by the Investigator.

c) Subjects at screening with the following abnormal laboratory values upon repeat testing are excluded:

i) Hemoglobin <9 g/dL

ii) Hematocrit < 30%

iii) Platelet count < 80,000/mm^3

iv) ALT or AST > ULN

v) Total bilirubin > 1.5X ULN

vi) aPTT or PT/INR > 1.2X ULN

d) Positive urine or saliva or plasma screen for drugs of abuse with exception for prescription medications

e) Positive blood screen for HIV-1 and HIV-2 antibody

4) Allergies and Adverse Drug Reaction

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

5) Other Exclusion Criteria

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

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

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

6.3 Lifestyle Restrictions

Subjects are to refrain from strenuous exercise, contact sports, and sunbathing from at least 5 day(s) prior to the first dose until study discharge.

1) Unless restricted by the clinical facility, subjects are permitted to smoke while residing at the clinical facility and on dialysis days.
2) Participants are not permitted to consume alcohol-containing beverages from 3 days prior to the first dose until study discharge.
3) Participants are not permitted to consume grapefruit-containing products from 3 days prior to the first dose until study discharge.
4) Participants are not permitted to consume more than two caffeine-containing beverages per day for the whole study duration.
5) On each study treatment day, patients are required to fast (nothing to eat or drink except water) for 4 hours prior to a standard meal, which will be consumed approximately 30 minutes prior to study drug administration. Patients may not drink water one hour before and after study drug administration except with dosing and the beverage provided with the pre-dose standard meal. Water may be consumed *ad libitum* at other times.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently [randomized/entered in the study/included in the analysis population]. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal

information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening or Lead-In Period

Participant Re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a pre-treatment failure (i.e., participant has not been randomized / has not been treated). If re-enrolled, the participant must be re-consented.

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

7. TREATMENT

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

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

- BMS-986177, unfractionated heparin (UFH) and Enoxaparin as IP/IMP.

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.

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. Not Applicable for this study.

Table 7.-1: Study treatments for CV010010

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS 986177/SDD 75% as the base[a]	100 mg or 300 mg	IP	Open label	Labeled bulk product in glass vials / white to off-white powder which may appear as lumps	Store at 2 C to 8 C, protected from light and moisture
UFH	Per Standard of Care	IP	Open label	Sourced by Site	Per Label
Enoxaparin	40 mg	IP	Open label	Sourced by Site	Per Label

[a] Compounding instructions will be provided separately to the site

7.1 Treatments Administered

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
Dose 1 BMS 986177/SDD 75% as the base[a]	100 mg	Single dose	PO
Dose 2 BMS 986177/SDD 75% as the base[a]	300 mg	Single dose	PO
UFH	Per SoC	(Standard of Care)	IV
Enoxaparin	40 mg	Single Dose (Standard of Care)	SC

[a] Compounding instructions will be provided separately to the site

Note: Per amendment/revised protocol 01, the BMS-986177 doses will be 100 mg (BMS dose 1) and 300 mg (BMS dose 2).

Study treatments will be dosed:

- BMS-986177: one single oral dose 3 hours prior beginning the HD session
- UFH: I.V. infusion to start within 10 minutes prior beginning the HD session. The dosage and duration of UFH use are at the discretion of the physicians and are per their institutional practice.
- Enoxaparin: one single dose (40 mg) by subcutaneous injection 3 hours prior beginning the HD session

At the time of dosing, BMS-986177, 240 mL of water will be administered to the participant along with his/her dose of study drug. The time of dose administration will be called "0" hour.

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

7.2 Method of Treatment Assignment

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

Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with 00001, (eg, 00001, 00002, 00003.... 00010). Sequential numbering may restart at 00001 for each participating site as the distinct patient identification number (PID) will ultimately be comprised of the site number and participant number, (eg, 0002 00001). Those enrolled participants meeting inclusion and exclusion criteria will be eligible to be randomized. Randomization numbers will be assigned prior to dosing.

Participants will not be replaced if they are discontinued from the study secondary to an adverse event unless the adverse event can be determined to be unrelated to treatment. If a participant is replaced after dosing then the replacement participant will be assigned the original participant's number plus 100. The replacement participant will receive the same treatment as the participant being replaced but a new randomization number will be assigned to him or her. For example, participant 4 would be replaced by Participant 104.

7.3 Blinding

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

7.4 Dosage Modification

Not Applicable

7.5 Preparation/Handling/Storage/Accountability

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

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

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

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

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

Compounding instructions for BMS-986177 will be provided separately to the site.

- Further guidance and information for final disposition of unused study treatment are provided in Appendix 2.

7.5.1 Retained Samples for Bioavailability / Bioequivalence

Not Applicable

7.6 Treatment Compliance

Study drug will be administered in the clinical facility. After administration of BMS-986177 an examination of the oral cavity is required to verify that a participant has swallowed the solution. The participant should drink the entire aliquot of water given to swallow the solution.

UFH and Enoxaparin will be administered by the healthcare staff at the clinical facility according to protocol and standard of care.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study drug administration in the study are described below. Medications taken within 4 weeks prior to study drug administration must be recorded on the CRF.

1) Use of any agent, including but not limited to anti-platelet agents (except aspirin), anticoagulants (except heparin for routine hemodialysis use), fish oil capsules, and ginko that is known to increase the potential for bleeding within 2 weeks prior to study drug administration. Use of non-steroidal anti-inflammatory compounds (NSAIDs) or aspirin within 1 week prior to study drug administration.
2) Exposure to any investigational drug or placebo within 4 weeks of study drug administration.
3) Use of acid controllers within two days of BMS-986177 study drug administration except those medications cleared by the BMS medical monitor. The use of acid controllers after BMS-986177 administration and after hemodialysis is allowed. The use of acid controllers is also allowed when enoxaparin or UFH are administered.
   a) Sodium bicarbonate is allowed during the study.
4) Use of strong and moderate CYP3A inhibitors within 1 week of enrollment including the following: the antifungals and antibiotics ketoconazole, fluconazole, itraconazole, miconazole, clotrimazole, erythromycin and clarithromycin; the calcium channel blockers diltiazem and verapamil; the HIV anti-virals delaviridine, indinavir, nelfinavir, ritonavir, and saquinavir; and the serotonin reuptake inhibitor fluoxetine. Use of CYP3A inducers such as carbamazapine, dexamethasone, phenobarbitol, phenytoin, rifampin, St John's Wort within 4 weeks of enrollment. Topical antifungal use is allowed.

Study patients may receive treatment with medications necessary for maintaining the clinical status of their condition as described in Inclusion Criteria.

Any concomitant therapies must be recorded on the CRF.

7.7.2 Other Restrictions and Precautions

Not Applicable

7.8 Treatment After the End of the Study

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

8. DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical 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 participant
- 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
- Pregnancy
- Overt bleeding producing a Hb decrease ≥ 2 g/dL in 24 hours
- Need for blood transfusion
- Overt bleeding which is retroperitoneal, intracranial, intra-spinal, intraocular, or intraarticular
- Any overt bleeding deemed by the investigator to necessitate discontinuation of trial medication
- Medical or surgical treatment for bleeding beyond the application of pressure or cold compress
- Need for surgery during the study period
- Need for treatment with an anticoagulant or antiplatelet agent during the study period, with the exception of heparin and enoxaparin use during HD
- Need for treatment with a strong CYP3A4 inhibitor or any CYP3A4 inducers
- Inability to continue on the hemodialysis treatment for the duration of the study
- Inability to comply with the protocol
- Occurrence in one of the BMS-986177 treatment arm or in the enoxaparin treatment arm of 5 or more patients with events of complete clotting of HD circuit causing premature interruption of the HD procedure. This will result in a discontinuation of that treatment arm. The randomized sequence for the following patients will not be changed, and the discontinued treatment arm will be replaced by standard of care (UFH) in the treatment sequence.

In case a subject experiences complete clotting leading to premature interruption of HD in the BMS-986177 arms, the HD session can be restarted using standard of care at the discretion of the study Investigator.

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

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

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

8.1.1 Post Study Treatment Study Follow-up

Participants who discontinue study treatment may continue to be followed.

8.2 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-Up

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

- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9. STUDY ASSESSMENTS AND PROCEDURES

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

9.1 Efficacy Assessments

Not Applicable

9.1.1 Imaging Assessment for the Study

Not Applicable

9.2 Adverse Events

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

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

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

SAE reporting specified in Appendix 3

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until [the follow-up contact], at the timepoints specified in the Schedule of Activities (Section 2).

Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

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

All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing.

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

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

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

9.2.2 Method of Detecting AEs and SAEs

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

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2 will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

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

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

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

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3

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

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

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

- Any laboratory test result that is clinically significant or meets the definition of an SAE

- Any laboratory test result abnormality that required the participant to have study treatment discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

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

Some coagulation tests (eg, aPTT,) are affected by the investigational drug and therefore changes in such tests are not to be considered as AEs but as PD biomarkers.

9.2.7 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details).

Potential drug induced liver injury is defined as:

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Appendix 3 for reporting details).

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times ULN

AND

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

AND

3) No other immediately apparent possible causes of 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.

9.2.8 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 non-serious or serious AE, as appropriate, and reported accordingly.

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 9.2).

9.4 Safety

Planned timepoints for all safety assessments are listed in the Schedule of Activities.

9.4.1 Physical Examinations

Refer to Schedule of Activities.

9.4.2 Vital signs

Refer to Schedule of Activities.

9.4.3 Electrocardiograms

Refer to Schedule of Activities.

9.4.4 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.
A local laboratory will perform the analyses and will provide reference ranges for these tests.

Results of clinical laboratory tests performed on Day -1 to -3 must be available prior to first dose of study drug.

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Coagulation	
PT	
aPTT	
INR	
Serum Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct bilirubin Alkaline phosphatase Lactate dehydrogenase (LDH) Creatinine Blood Urea Nitrogen (BUN) Uric acid Fasting glucose (if possible)	Total Protein Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatine kinase

Urine Dipstick
Blood (only if the participant is able to produce urine)
Serology
HIV-1 and -2 antibody (screening only)
Other Analyses
Test for drugs of abuse (urine or saliva or plasma)
Alcohol breathalyzer
Fecal occult blood (screening and after each treatment period if sample can be obtained)
Pregnancy test (urine or blood)- WOCBP only

9.4.5 Suicidal Risk Monitoring

Not Applicable

9.4.6 Imaging Safety Assessment

Not Applicable

9.5 Pharmacokinetic

Pharmacokinetics of BMS-986177 will be derived from plasma concentration versus time. The pharmacokinetic parameters to be assessed include:

Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
AUC(0-T)	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC(INF)	Area under the plasma concentration-time curve from time zero extrapolated to infinite time
AUC(0-48)	Area under the plasma concentration-time curve from time zero to 48 hours
T-HALF	Terminal plasma half-life
fu	Fraction of unbound drug
Cmaxfu	Maximum observed plasma concentration of free drug
AUC(0-T)fu	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration of free drug
AUC(INF)fu	Area under the plasma concentration-time curve from time zero extrapolated to infinite time of free drug
AUC(3-7)	Area under the plasma concentration-time curve from 3 to 7 hours. (ie, during dialysis. Determined from blood samples entering and exiting the dialyzer)
%DR	Percent dose of BMS-986177 recovered in dialysate (%)
CLD	Dialysate clearance of drug from plasma Cumulative amount in dialysate over 3 to 7 hours postdose divided by plasma AUC(3-7)

Individual participant pharmacokinetic parameter values will be derived by non-compartmental methods by a validated pharmacokinetic analysis program. Actual times will be used for the analyses.

Table 9.5-1: Pharmacokinetic Sampling Schedule for BMS-986177

Day of Sample Collection when BMS-986177 is dosed	Event	Time Relative to BMS-986177 Dose) Hour: Min	BMS-986177 Blood Sample for PK	BMS-986177 Protein Binding Sample	BMS-986177 Dialysate Sample
BMS-986177 dosing day (depending on randomization sequence it may be study day 1, 5, 8, or 12)	predose	00:00	X[a]		
	postdose	1:00	X		
	hemodialysis start[c]	3:00	X[b]		X (3-7) [e]
		3:30	X[b]		
		4:00	X[b]		
		5:00	X[b]	X	
		6:00	X[b]		
	hemodialysis stop[c]	7:00	X[b]		
		8:00	X		
		9:00	X		
24 to 72 hours after BMS-986177 dosing		24:00 - 72:00 [d]	X		

Note: Day 1, 5, 8, and 12 is the start of Period 1, 2, 3, and 4, respectively. Hemodialysis duration could range from 3 to 4 hours but should be consistent on the days when study drug is administered.

[a] Sample to be obtained prior to study drug administration.

[b] Two blood samples are obtained at each of these time points (one sample is collected prior to entering the dialyzer and the second sample is collected after exiting the dialyzer) for Periods for BMS-986177 only

[c] Sample to be collected from the blood prior to entering the dialyzer.

[d] Single sample between days 2-4, days 6-8, days 9-11, and days 13-15.

[e] Dialysate sample to be collected hourly between 3 to 7 hr during the hemodialysis session.

The plasma samples will be analyzed for BMS-986177 by a validated LC/MS/MS assay. In addition, plasma samples will be archived for potential metabolite analysis, if the need arises and to the extent possible.

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

After the scheduled PK analyses are completed, residual plasma may be used for metabolite profiling. If these analyses are conducted, they will be reported separately from the CSR.

9.6 Pharmacodynamics

Blood will be drawn at the times indicated in Table 9.6-1 and Table 9.6-2, for the measurement of pharmacodynamic markers (PD): aPTT, and Factor XI clotting activity (FXIc) for BMS-986177, aPTT and Anti-Xa for heparin and Enoxaparin. Further details of blood collection and processing will be provided to the site in the procedure manual.

Table 9.6-1: Pharmacodynamic Sampling Schedule for dialysis session with BMS-986177 and Enoxaparin

Event	Time (Relative To BMS-BMS-986177 or Enoxaparin Dose) Hour: Min	Blood Sample for aPTT, FXIc (BMS-986177 day only)[a]	Blood Sample for aPTT and anti-Xa (Enoxaparin day only)[a]
predose	00:00	X	X
	01:00	X	X
Hemodialysis start	03:00	X[a]	X[a]
	04:00	X[a]	X[a]
	05:00	X[a]	X[a]
	06:00	X[a]	X[a]
Hemodialysis stop	07:00	X[a]	X[a]
	08:00	X	X
	09:00	X	X
24 to 72 hours after BMS-986177 dosing	24:00 - 72:00[b]	X	

Note: Hemodialysis duration could range from 3 to 4 hours but should be consistent on the days when study drug is administered.

[a] Blood sample is collected prior to entering the dialyzer.

[b] Single sample between days 2-4, days 6-8, days 9-11, and days 13-15.

Table 9.6-2: Pharmacodynamic Sampling Schedule for dialysis session with UFH

Event	Time (Relative To UFH Dose) Hour: Min	Blood Sample for aPTT and anti-Xa (UFH days only)
Predose/ Hemodialysis start	00:00	X[a]
	01:00	X[a]
	02:00	X[a]
	03:00	X[a]
Hemodialysis stop	04:00	X[a]
	05:00	X
	06:00	X

Note: Hemodialysis duration could range from 3 to 4 hours but should be consistent on the days when study drug is administered.

[a] Blood sample is collected prior to entering the dialyzer.

9.7 Pharmacogenomics

9.7.1 Genotyping and ADME Sampling

A 6-mL whole blood sample will be drawn at baseline for dosed participants as indicated in Section 2 Schedule of Activities) for potential analysis of DNA variants in ADME-related genes (see Appendix 5) which contains the lists of ADME-related genes from http://pharmaadme.org), and/or hemostasis and thrombosis related genes. Further details of blood collection and processing will be provided to the site in the procedure manual.

[redacted]

9.8.1 Additional Research Collection

Additional research collections and retention are mandatory for all subjects, except where prohibited by local laws or regulations.

This protocol will include residual sample storage for additional research (AR).

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

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

Residual plasma from PD and biomarker collections (see Table 9.6-1, Table 9.6-2, Table 9.8-1, and Table 9.8-2) will also be retained for additional research purposes.

Samples will be securely stored by the BMS Biorepository in NJ or at a BMS approved third party storage management facility.

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

Additional research samples will be retained for 15 years or the maximum allowed by applicable law. No additional sampling is required for residual collections.

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

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

Sample Type	Timepoints for which residual samples will be retained
D-dimer, F1.2 and exploratory sample	All time points as in Table 9.8-1 and Table 9.8-2
aPTT, FXIc, anti-Xa	All time points as in Table 9.6-1 and Table 9.6-2

9.8.2 Other Assessments

Not Applicable

9.9 Health Economics OR Medical Resource Utilization and Health Economics

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

10. STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

Although the number of patients is not based on statistical power considerations, administration of BMS-986177 to 32 subjects with ESRD would provide over 80% probability of observing at least one occurrence of any adverse event that would occur with incidence of 5% in the population from which the sample is drawn

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All subjects who sign informed consent
Randomized	All subjects who are randomized to the study including the subjects who replace the discontinuing randomized subjects
Evaluable	All randomized subjects who take at least 1 dose of study treatment.
Safety	All randomized subjects who take at least 1 dose of study treatment.
Pharmacokinetic	All participants who receive BMS-986177 from whom PK parameter data were obtained before and after HD.
Pharmacodynamic	Is a subset of the Safety Population and includes all subjects who received at least 1 dose of study medication and had any available PD or biomarker data.

10.3 Statistical Analyses

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

10.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	NA

10.3.2 Safety Analyses

Safety analyses will be performed on all safety assessments.

Endpoint	Statistical Analysis Methods
Primary	Descriptive summaries will be presented for continuous variables using number of subjects (N), mean, standard deviation (SD), median, minimum and maximum. Descriptive summaries for categorical variables will utilize counts and percentages. All recorded AEs will be listed and tabulated by system organ class and preferred term, and treatment. Changes from baseline in vital signs, ECG, and clinical laboratory test results will be listed and summarized by treatment and time point. Any significant physical examination findings and any marked abnormal clinical laboratory test results will be listed. Electrocardiogram readings will be summarized by time point, and investigator-identified abnormalities, if present, will be listed.

10.3.3 Pharmacokinetic Analyses

Endpoint	Statistical Analysis Methods
See section 9.5 for all PK parameters	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.

[redacted]

Results of DNA variants and other exploratory measures may not be reported in the CSR.

10.3.5 Interim Analyses

Not Applicable

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ADME	Absorption, distribution, metabolism, excretion
AE	adverse event
ACLS	advanced cardiac life support
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ARIC	Atherosclerosis Risk in Communities
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
β-HCG	beta-human chorionic gonadotrophin
BID, bid	bis in die, twice daily
BLQ	below limit of quantification
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
Ca^{++}	calcium
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
$C1^{-}$	chloride
CLcr	creatinine clearance
CLD	Dialysate clearance of drug from plasma/serum

Term	Definition
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	minimum observed concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
CV	coefficient of variation
CYP	cytochrome p-450
D/C	discontinue
dL	deciliter
DMC	Data monitoring committee
DRt, DR	Total amount recovered in dialysate
%DRt, %DR	Total percent of administered dose recovered in dialysate
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} Edition)
DVT	deep vein thrombosis
EC20, EC50, EC80	Effective concentration at 20%, 50%, 80%
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg, e.g.	exempli gratia (for example)
ESR	Expedited Safety Report
ESRD	end-stage renal disease
F	bioavailability
FIH	First in human
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
fu	fraction of unbound drug
FXI	Factor XI
FXIa	Factor XIa

Term	Definition
FXIc	Factor XI clotting activity
g	gram
GC	gas chromatography
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO_3^-	bicarbonate
HD	hemodialysis
HIT	heparin-induced thrombocytopenia
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
IB	investigator brochure
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ie, i.e.	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
INR	international normalized ratio
IRB	Institutional Review Board
IU	International Unit
IUD	intrauterine devices
IV, I.V.	intravenous
K	slope of the terminal phase of the log concentration-time curve
K_3EDTA	potassium ethylenediaminetetraacetic acid
K^+	potassium

Term	Definition
Ki	inhibition constant
kg	kilogram
Kt/V	Number used to quantify hemodialysis and peritoneal dialysis treatment adequacy. Assessment includes: pre-dialysis blood BUN, post-dialysis blood BUN, ultrafiltration volume, post-dialysis body weight, duration of dialysis session.
L	liter
LAM	lactation amenorrhea method
LC	liquid chromatography
LDH	lactate dehydrogenase
LFTs	liver function tests
LMWH	low molecular weight heparin
MAD	multiple ascending dose
mg	milligram
Mg^{++}	magnesium
min	minute
mL	milliliter
mmHg	millimeters of mercury
MR	medical research
MS	mass spectrometry
µg	microgram
N	number of subjects or observations
Na^{+}	sodium
N/A, NA	not applicable
ng	nanogram
NIMP	non-investigational medicinal products
NOAEL	no-observed-adverse-effect-level
NSAID	nonsteroidal anti-inflammatory drug
P2Y12	Gi class of a group of G protein-coupled (GPCR) purinergic receptors and is a chemoreceptor for adenosine diphosphate (ADP)
PD	pharmacodynamics

Term	Definition
PID	patient identification number
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PT	prothrombin time
PTT	partial thromboplastin time
QC	quality control
QD, qd	quaque die, once daily
RATIO	Risk of Arterial Thrombosis In relation to Oral contraceptives
RBC	red blood cell
SAD	single ascending dose
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SDD	spray dry dispersion
SOA	schedule of activities
SOC	standard of care
SOP	Standard Operating Procedures
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
T-HALF	Half life
TID, tid	ter in die, three times a day
Tmax, TMAX	time of maximum observed concentration
UFH	unfractionated heparin
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
WNOCBP	women **not** of childbearing potential
x g	times gravity

APPENDIX 2 STUDY GOVERANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

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

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

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

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

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

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

SOURCE DOCUMENTS

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

(EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

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

STUDY TREATMENT RECORDS

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

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

If	Then
a specialty pharmacy)	SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant 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.

CASE REPORT FORMS

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

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

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

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

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

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

MONITORING

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

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

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

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

RECORDS RETENTION

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

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

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

RETURN OF STUDY TREATMENT

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

If..	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as

	required for safety, or to meet local regulations (e.g., cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

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

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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

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

It is however, the investigator's or designee's responsibility to arrange for disposal of all empty study treatment containers, 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 return of full or partially used study treatments supplied by BMS or its vendors will be arranged by the responsible Study Monitor.

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
- Participant recruitment (e.g., among the top quartile of enrollers)
- Involvement in trial design
- Other criteria (as determined by the study team)

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

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

ADVERSE EVENTS

Adverse Event Definition:
An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study 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.

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: ○ a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) ○ elective surgery, planned prior to signing consent ○ admissions as per protocol for a planned medical/surgical procedure ○ routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) ○ medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases ○ admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) ○ admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect

is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 8.1.1 for the definition of potential DILI.)

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study treatment is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 9.2.5 for reporting pregnancies).

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

EVALUATING AES AND SAES

Assessment of Causality

The 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.

Follow-up of AEs and SAEs

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

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

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

Any one of the approved methods of contraception (highly effective and/or less than highly effective) listed below is required during study duration plus 5 half-lives of study treatment

BMS-986177 (2 days) plus 30 days (duration of ovulatory cycle) for a total of 32 days post-treatment completion or after treatment has been discontinued.

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

Table 1-1: Methods of Contraception

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of >1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide

Table 1-1: Methods of Contraception

• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal(coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, hormonal methods of contraception can be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

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

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

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until the end of relevant systemic exposure defined as 2 days after the end of treatment in the male participant with amendment/revised protocol 02 (See Section 6.1 Inclusion Criteria).
- Female partners of males participating in the study to consider use of effective methods of contraception (see Table 1-1) until the end of relevant systemic exposure, defined as 2 days after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 2 days after the end of treatment.
- Refrain from donating sperm for the duration of the study treatment and for 2 days after the end of treatment with amendment/revised protocol 02 (See Section 6.1 Inclusion Criteria).

COLLECTION OF PREGNANCY INFORMATION

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

APPENDIX 5 CORE ADME GENE LIST (FROM HTTP://PHARMAADME.ORG)

Gene Symbol	Full Gene Name	Class
ABCB1	ATP-binding cassette, sub-family B (MDR/TAP), member 1	Transporter
ABCC2	ATP-binding cassette, sub-family C (CFTR/MRP), member 2	Transporter
ABCG2	ATP-binding cassette, sub-family G (WHITE), member 2	Transporter
CYP1A1	cytochrome P450, family 1, subfamily A, polypeptide 1	Phase I
CYP1A2	cytochrome P450, family 1, subfamily A, polypeptide 2	Phase I
CYP2A6	cytochrome P450, family 2, subfamily A, polypeptide 6	Phase I
CYP2B6	cytochrome P450, family 2, subfamily B, polypeptide 6	Phase I
CYP2C19	cytochrome P450, family 2, subfamily C, polypeptide 19	Phase I
CYP2C8	cytochrome P450, family 2, subfamily C, polypeptide 8	Phase I
CYP2C9	cytochrome P450, family 2, subfamily C, polypeptide 9	Phase I
CYP2D6	cytochrome P450, family 2, subfamily D, polypeptide 6	Phase I
CYP2E1	cytochrome P450, family 2, subfamily E, polypeptide 1	Phase I
CYP3A4	cytochrome P450, family 3, subfamily A, polypeptide 4	Phase I
CYP3A5	cytochrome P450, family 3, subfamily A, polypeptide 5	Phase I
DPYD	dihydropyrimidine dehydrogenase	Phase I
GSTM1	glutathione S-transferase M1	Phase II
GSTP1	glutathione S-transferase pi	Phase II
GSTT1	glutathione S-transferase theta 1	Phase II
NAT1	N-acetyltransferase 1 (arylamine N-acetyltransferase)	Phase II
NAT2	N-acetyltransferase 2 (arylamine N-acetyltransferase)	Phase II
SLC15A2	solute carrier family 15 (H+/peptide transporter), member 2	Transporter
SLC22A1	solute carrier family 22 (organic cation transporter), member 1	Transporter
SLC22A2	solute carrier family 22 (organic cation transporter), member 2	Transporter
SLC22A6	solute carrier family 22 (organic anion transporter), member 6	Transporter
SLCO1B1	solute carrier organic anion transporter family, member 1B1	Transporter
SLCO1B3	solute carrier organic anion transporter family, member 1B3	Transporter
SULT1A1	sulfotransferase family, cytosolic, 1A, phenol-preferring, member1	Phase II
TPMT	thiopurine S-methyltransferase,	Phase II

Gene Symbol	Full Gene Name	Class
UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1	Phase II
UGT2B15	UDP glucuronosyltransferase 2 family, polypeptide B15	Phase II
UGT2B17	UDP glucuronosyltransferase 2 family, polypeptide B17	Phase II
UGT2B7	UDP glucuronosyltransferase 2 family, polypeptide B7	Phase II

EXTENDED ADME GENE LIST:

Gene Symbol	Full Gene Name	Class
ABCB8	ATP-binding cassette, sub-family B (MDR/TAP), member 8	Transporter
ABCC12	ATP-binding cassette, sub-family C (CFTR/MRP), member 12	Transporter
ABCC3	ATP-binding cassette, sub-family C (CFTR/MRP), member 3	Transporter
ABCC4	ATP-binding cassette, sub-family C (CFTR/MRP), member 4	Transporter
AHR	aryl hydrocarbon receptor	Modifier
ALDH4A1	aldehyde dehydrogenase 4 family, member A1	Phase I
ALDH5A1	aldehyde dehydrogenase 5 family, member A1	Phase I
ALDH6A1	aldehyde dehydrogenase 6 family, member A1	Phase I
CES1	carboxylesterase 1 (monocyte/macrophage serine esterase 1)	Phase I
CES2	carboxylesterase 2 (intestine, liver)	Phase I
CYP7A1	cytochrome P450, family 7, subfamily A, polypeptide 1	Phase I
EPHX1	epoxide hydrolase 1, microsomal (xenobiotic)	Phase I
FMO3	flavin containing monooxygenase 3	Phase I
GSTA1	glutathione S-transferase A1	Phase II
GSTA2	glutathione S-transferase A2	Phase II
GSTA3	glutathione S-transferase A3	Phase II
GSTA4	glutathione S-transferase A4	Phase II
GSTA5	glutathione S-transferase A5	Phase II
GSTM2	glutathione S-transferase M2 (muscle),glutathione S-transferase M4	Phase II
GSTM3	glutathione S-transferase M3 (brain)	Phase II
GSTM4	glutathione S-transferase M4	Phase II
GSTO1	glutathione S-transferase omega 1,glutathione S-transferase omega 2	Phase II
GSTO2	glutathione S-transferase omega 2	Phase II
GSTT2	glutathione S-transferase theta 2	Phase II
SLC10A1	solute carrier family 10 (sodium/bile acid cotransporter family), member 1	Transporter

Gene Symbol	Full Gene Name	Class
SLC15A1	solute carrier family 15 (oligopeptide transporter), member 1	Transporter
SLC22A11	solute carrier family 22 (organic anion/cation transporter), member 11	Transporter
SLC22A8	solute carrier family 22 (organic anion transporter), member 8	Transporter
SLC7A5	solute carrier family 7 (cationic amino acid transporter, y+ system), member 5	Transporter
SLCO1A2	solute carrier organic anion transporter family, member 1A2	Transporter
SLCO2B1	solute carrier organic anion transporter family, member 2B1	Transporter
SULT1A2	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 2	Phase II
SULT1A3	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 3	Phase II
SULT1B1	sulfotransferase family, cytosolic, 1B, member 1	Phase II
UGT1A3	UDP glucuronosyltransferase 1 family, polypeptide A3	Phase II
UGT1A6	UDP glucuronosyltransferase 1 family, polypeptide A6	Phase II
UGT1A7	UDP glucuronosyltransferase 1 family, polypeptide A7	Phase II
UGT1A8	UDP glucuronosyltransferase 1 family, polypeptide A8	Phase II
UGT1A9	UDP glucuronosyltransferase 1 family, polypeptide A9	Phase II
UGT2A1	UDP glucuronosyltransferase 2 family, polypeptide A1	Phase II
UGT2B11	UDP glucuronosyltransferase 2 family, polypeptide B11	Phase II
UGT2B28	UDP glucuronosyltransferase 2 family, polypeptide B28	Phase II
UGT2B4	UDP glucuronosyltransferase 2 family, polypeptide B4	Phase II
ABCA1	ATP-binding cassette, sub-family A (ABC1), member 1	Transporter
ABCA4	ATP-binding cassette, sub-family A (ABC1), member 4	Transporter
ABCB11	ATP-binding cassette, sub-family B (MDR/TAP), member 11	Transporter
ABCB4	ATP-binding cassette, sub-family B (MDR/TAP), member 4	Transporter
ABCB5	ATP-binding cassette, sub-family B (MDR/TAP), member 5	Transporter
ABCB6	ATP-binding cassette, sub-family B (MDR/TAP), member 6	Transporter

Gene Symbol	Full Gene Name	Class
ABCB7	ATP-binding cassette, sub-family B (MDR/TAP), member 7	Transporter
ABCC1	ATP-binding cassette, sub-family C (CFTR/MRP), member 1	Transporter
ABCC10	ATP-binding cassette, sub-family C (CFTR/MRP), member 10	Transporter
ABCC11	ATP-binding cassette, sub-family C (CFTR/MRP), member 11	Transporter
ABCC5	ATP-binding cassette, sub-family C (CFTR/MRP), member 5	Transporter
ABCC6	ATP-binding cassette, sub-family C (CFTR/MRP), member 6	Transporter
ABCC8	ATP-binding cassette, sub-family C (CFTR/MRP), member 8	Transporter
ABCC9	ATP-binding cassette, sub-family C (CFTR/MRP), member 9	Transporter
ABCG1	ATP-binding cassette, sub-family G (WHITE), member 1	Transporter
ADH1A	alcohol dehydrogenase 1A (class I), alpha polypeptide	Phase I
ADH1B	alcohol dehydrogenase IB (class I), beta polypeptide	Phase I
ADH1C	alcohol dehydrogenase 1C (class I), gamma polypeptide	Phase I
ADH4	alcohol dehydrogenase 4 (class II), pi polypeptide	Phase I
ADH5	alcohol dehydrogenase 5 (class III), chi polypeptide, methionyl aminopeptidase 1	Phase I
ADH6	alcohol dehydrogenase 6 (class V)	Phase I
ADH7	alcohol dehydrogenase 7 (class IV), mu or sigma polypeptide	Phase I
ALDH1A1	aldehyde dehydrogenase 1 family, member A1	Phase I
ALDH1A2	aldehyde dehydrogenase 1 family, member A2	Phase I
ALDH1A3	aldehyde dehydrogenase 1 family, member A3	Phase I
ALDH1B1	aldehyde dehydrogenase 1 family, member B1	Phase I
ALDH2	aldehyde dehydrogenase 2 family (mitochondrial)	Phase I
ALDH3A1	aldehyde dehydrogenase 3 family, memberA1	Phase I
ALDH3A2	aldehyde dehydrogenase 3 family, member A2	Phase I
ALDH3B1	aldehyde dehydrogenase 3 family, member B1	Phase I
ALDH3B2	aldehyde dehydrogenase 3 family, member B2	Phase I

Gene Symbol	Full Gene Name	Class
ALDH7A1	aldehyde dehydrogenase 7 family, member A1	Phase I
ALDH8A1	aldehyde dehydrogenase 8 family, member A1	Phase I
ALDH9A1	aldehyde dehydrogenase 9 family, member A1	Phase I
AOX1	aldehyde oxidase 1	Phase I
ARNT	aryl hydrocarbon receptor nuclear translocator	Modifier
CBR1	carbonyl reductase 1	Phase I
CBR3	carbonyl reductase 3	Phase I
CDA	cytidine deaminase	Modifier
CYB5R3	cytochrome b5 reductase 3	Phase I
CYP11A1	cytochrome P450, family 11, subfamily A, polypeptide 1	Phase I
CYP11B1	cytochrome P450, family 11, subfamily B, polypeptide 1	Phase I
CYP11B2	cytochrome P450, family 11, subfamily B, polypeptide 2	Phase I
CYP17A1	cytochrome P450, family 17, subfamily A, polypeptide 1	Phase I
CYP1B1	cytochrome P450, family 1, subfamily B, polypeptide 1	Phase I
CYP20A1	cytochrome P450, family 20, subfamily A, polypeptide 1	Phase I
CYP20A1	cytochrome P450, family 20, subfamily A, polypeptide 1	Phase I
CYP21A2	cytochrome P450, family 21, subfamily A, polypeptide 2	Phase I
CYP24A1	cytochrome P450, family 24, subfamily A, polypeptide 1	Phase I
CYP26A1	cytochrome P450, family 26, subfamily A, polypeptide 1	Phase I
CYP27A1	cytochrome P450, family 27, subfamily A, polypeptide 1	Phase I
CYP2A13	cytochrome P450, family 2, subfamily A, polypeptide 13	Phase I
CYP2A7	cytochrome P450, family 2, subfamily A, polypeptide 7	Phase I
CYP2C18	cytochrome P450, family 2, subfamily C, polypeptide 18	Phase I
CYP2F1	cytochrome P450, family 2, subfamily F, polypeptide 1	Phase I
CYP2J2	cytochrome P450, family 2, subfamily J, polypeptide 2	Phase I
CYP39A1	cytochrome P450, family 39, subfamily A, polypeptide 1	Phase I
CYP3A43	cytochrome P450, family 3, subfamily A, polypeptide 43	Phase I
CYP3A7	cytochrome P450, family 3, subfamily A, polypeptide 7	Phase I
CYP4B1	cytochrome P450, family 4, subfamily B, polypeptide 1	Phase I
CYP4F11	cytochrome P450, family 4, subfamily F, polypeptide 11	Phase I
CYP51A1	cytochrome P450, family 51, subfamily A, polypeptide 1	Phase I
EPHX2	epoxide hydrolase 2, cytoplasmic	Phase I
FMO1	flavin containing monooxygenase 1	Phase I
FMO2	flavin containing monooxygenase 2	Phase I

Gene Symbol	Full Gene Name	Class
FMO4	flavin containing monooxygenase 4	Phase I
FMO5	flavin containing monooxygenase 5	Phase I
GPX2	glutathione peroxidase 2 (gastrointestinal)	Phase I
GPX3	glutathione peroxidase 3 (plasma)	Phase I
GPX7	glutathione peroxidase 7	Phase I
GSR	glutathione reductase	Phase I
GSTK1	glutathione S-transferase kappa 1	Phase II
GSTM5	glutathione S-transferase M5	Phase II
GSTZ1	glutathione transferase zeta 1 (maleylacetoacetate isomerase)	Phase II
NNMT	nicotinamide N-methyltransferase	Phase II
NR1I2	nuclear receptor subfamily 1, group I, member 2	Modifier
NR1I3	nuclear receptor subfamily 1, group I, member 3	Modifier
PNMT	phenylethanolamine N-methyltransferase	Phase II
PON1	paraoxonase 1	Phase I
PON2	paraoxonase 2	Phase I
PON3	paraoxonase 3	Phase I
POR	P450 (cytochrome) oxidoreductase	Modifier
PPARD	peroxisome proliferative activated receptor, delta	Modifier
PPARG	peroxisome proliferative activated receptor, gamma	Modifier
RXRA	retinoid X receptor, alpha	Modifier
SLC10A2	solute carrier family 10 (sodium/bile acid cotransporter family), member 2	Transporter
SLC13A1	solute carrier family 13 (sodium/sulfate symporters), member 1	Transporter
SLC13A2	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 2	Transporter
SLC13A3	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 3	Transporter
SLC16A1	solute carrier family 16 (monocarboxylic acid Transporter), member 1	Transporter
SLC19A1	solute carrier family 19 (folate transporter), member 1	Transporter

Gene Symbol	Full Gene Name	Class
SLC22A10	solute carrier family 22 (organic anion/cation transporter), member 10	Transporter
SLC22A12	solute carrier family 22 (organic anion/cation transporter), member 12	Transporter
SLC22A13	solute carrier family 22 (organic cation transporter), member 13	Transporter
SLC22A14	solute carrier family 22 (organic cation transporter), member 14	Transporter
SLC22A15	solute carrier family 22 (organic cation transporter), member 15	Transporter
SLC22A16	solute carrier family 22 (organic cation transporter), member 16	Transporter
SLC22A17	solute carrier family 22 (organic cation transporter), member 17	Transporter
SLC22A18	solute carrier family 22 (organic cation transporter), member 18	Transporter
SLC22A18AS	solute carrier family 22 (organic cation transporter), member 18 antisense	Transporter
SLC22A3	solute carrier family 22 (extraneuronal monoamine transporter), member 3	Transporter
SLC22A4	solute carrier family 22 (organic cation transporter), member 4	Transporter
SLC22A5	solute carrier family 22 (organic cation transporter), member 5	Transporter
SLC22A7	solute carrier family 22 (organic anion transporter), member 7	Transporter
SLC22A9	solute carrier family 22 (organic anion/cation transporter), member 9	Transporter
SLC27A1	solute carrier family 27 (fatty acid transporter), member 1	Transporter
SLC28A1	solute carrier family 28 (sodium-coupled nucleoside transporter), member 1	Transporter
SLC28A2	solute carrier family 28 (sodium-coupled nucleoside transporter), member 2	Transporter

Gene Symbol	Full Gene Name	Class
SLC28A3	solute carrier family 28 (sodium-coupled nucleoside transporter), member 3	Transporter
SLC29A1	solute carrier family 29 (nucleoside Transporter), member 1	Transporter
SLC29A2	solute carrier family 29 (nucleoside Transporter), member 2	Transporter
SLC2A4	solute carrier family 2 (facilitated glucose transporter), member 4	Transporter
SLC2A5	solute carrier family 2 (facilitated glucose/fructose transporter), member 5	Transporter
SLC5A6	solute carrier family 5 (sodium-dependent vitamin transporter)	Transporter
SLC6A6	solute carrier family 6 (neurotransmitter transporter, taurine), member 6	Transporter
SLC7A8	solute carrier family 7 (cationic amino acid transporter, y+ system), member 8	Transporter
SLCO1C1	solute carrier organic anion transporter family, member 1C1	Transporter
SLCO2A1	solute carrier organic anion transporter family, member 2A1	Transporter
SLCO3A1	solute carrier organic anion transporter family, member 3A1	Transporter
SLCO4A1	solute carrier organic anion transporter family, member 4A1	Transporter
SLCO4C1	solute carrier organic anion transporter family, member 4C1	Transporter
SLCO5A1	solute carrier organic anion transporter family, member 5A1	Transporter
SLCO6A1	solute carrier organic anion transporter family, member 6A1	Transporter
SULT1C1	sulfotransferase family, cytosolic, 1C, member 1	Phase II
SULT1C2	sulfotransferase family, cytosolic, 1C, member 2	Phase II
SULT1E1	sulfotransferase family 1E, estrogen-preferring, member 1	Phase II

Gene Symbol	Full Gene Name	Class
SULT2A1	sulfotransferase family, cytosolic, 2A, DHEA preferring, member 1	Phase II
SULT2B1	sulfotransferase family, cytosolic, 2B, member 1	Phase II
TAP1	transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	Transporter
UGT1A10	UDP glucuronosyltransferase 1 family, polypeptide A10	Phase II
UGT1A4	UDP glucuronosyltransferase 1 family, polypeptide A4	Phase II
UGT1A5	UDP glucuronosyltransferase 1 family, polypeptide A5	Phase II
UGT2B10	UDP glucuronosyltransferase 2 family, polypeptide B10	Phase II
ABCC13	ATP-binding cassette, sub-family C (CFTR/MRP), member 13	Transporter
ARSA	arylsulfatase A	Modifier
CAT	catalase	Modifier
CHST8	carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 8	Phase II
CYP19A1	cytochrome P450, family 19, subfamily A, polypeptide 1	Phase I
CYP26C1	cytochrome P450, family 26, subfamily C, polypeptide 1	Phase I
CYP27B1	cytochrome P450, family 27, subfamily B, polypeptide 1	Phase I
CYP2R1	cytochrome P450, family 2, subfamily R, polypeptide 1	Phase I
CYP2S1	cytochrome P450, family 2, subfamily S, polypeptide 1	Phase I
CYP46A1	cytochrome P450, family 46, subfamily A, polypeptide 1	Phase I
CYP4A11	cytochrome P450, family 4, subfamily A, polypeptide 11	Phase I
CYP4F12	cytochrome P450, family 4, subfamily F, polypeptide 12	Phase I
CYP4F2	cytochrome P450, family 4, subfamily F, polypeptide 2	Phase I
CYP4F3	cytochrome P450, family 4, subfamily F, polypeptide 3	Phase I
CYP4F8	cytochrome P450, family 4, subfamily F, polypeptide 8	Phase I
CYP4Z1	cytochrome P450, family 4, subfamily Z, polypeptide 1	Phase I
CYP7B1	cytochrome P450, family 7, subfamily B, polypeptide 1	Phase I
CYP8B1	cytochrome P450, family 8, subfamily B, polypeptide 1	Phase I
DHRS13	dehydrogenase/reductase (SDR family) member 13	Phase I
DHRS2	dehydrogenase/reductase (SDR family) member 2	Phase I
GPX1	glutathione peroxidase 1	Phase I
GPX4	glutathione peroxidase 4 (phospholipid hydroperoxidase)	Phase I
GPX5	glutathione peroxidase 5 (epididymal androgen-related protein)	Phase I

Gene Symbol	Full Gene Name	Class
GPX6	glutathione peroxidase 6 (olfactory)	Phase I
GSS	glutathione synthetase	Phase I
GSTCD	glutathione S-transferase, C-terminal domain containing	Phase II
HNF4A	hepatocyte nuclear factor 4, alpha	Modifier
HNMT	histamine N-methyltransferase	Phase II
HSD11B1	hydroxysteroid (17-beta) dehydrogenase 11	Phase I
HSD17B11	hydroxysteroid (17-beta) dehydrogenase 11	Phase I
HSD17B14	hydroxysteroid (17-beta) dehydrogenase 14	Phase I
LOC731356	similar to dehydrogenase/reductase (SDR family) member 4 like 2	Phase I
MGST1	microsomal glutathione S-transferase 1	Phase II
MGST2	microsomal glutathione S-transferase 2	Phase II
MGST3	microsomal glutathione S-transferase 3	Phase II
MPO	myeloperoxidase	Modifier
NOS1	nitric oxide synthase 1 (neuronal)	Phase I
NOS2A	nitric oxide synthase 2A (inducible, hepatocytes)	Phase I
NOS3	nitric oxide synthase 3 (endothelial cell)	Phase I
PPARA	peroxisome proliferator-activated receptor alpha	Modifier
SERPINA7	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 7	Modifier
SLC7A7	solute carrier family 7 (cationic amino acid transporter, y+ system), member 7	Transporter
SOD1	superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 [adult])	Modifier
SOD2	superoxide dismutase 2, mitochondrial	Modifier
SOD3	superoxide dismutase 3, extracellular precursor	Modifier
SULF1	sulfatase 1	Phase I
SULT4A1	sulfotransferase family 4A, member 1	Phase II
TAP2	transporter 2, ATP-binding cassette, sub-family B (MDR/TAP)	Transporter
UGT8	UDP glycosyltransferase 8 (UDP-galactose ceramide galactosyltransferase)	Phase II

Gene Symbol	Full Gene Name	Class
XDH	xanthine dehydrogenase	Phase I
ADHFE1	alcohol dehydrogenase, iron containing, 1	Phase I
CHST1	carbohydrate (keratan sulfate Gal-6) sulfotransferase 1	Phase II
CHST10	carbohydrate sulfotransferase 10	Phase II
CHST11	carbohydrate (chondroitin 4) sulfotransferase 11	Phase II
CHST12	carbohydrate (chondroitin 4) sulfotransferase 12	Phase II
CHST13	carbohydrate (chondroitin 4) sulfotransferase 13	Phase II
CHST2	carbohydrate (N-acetylglucosamine-6-O) sulfotransferase 2	Phase II
CHST3	carbohydrate (chondroitin 6) sulfotransferase 3	Phase II
CHST4	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 4	Phase II
CHST5	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 5	Phase II
CHST6	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 6	Phase II
CHST7	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 7	Phase II
CHST9	carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 9	Phase II
CYP2D7P1	cytochrome P450, family 2, subfamily D, polypeptide 7 pseudogene 1	Phase I
DDO	D-aspartate oxidase	Phase I
DHRS1	dehydrogenase/reductase (SDR family) member 1	Phase I
DHRS12	dehydrogenase/reductase (SDR family) member 12	Phase I
DHRS3	dehydrogenase/reductase (SDR family) member 3	Phase I
DHRS4	dehydrogenase/reductase (SDR family) member 4	Phase I
DHRS4L1	dehydrogenase/reductase (SDR family) member 4 like 1	Phase I
DHRS4L2	dehydrogenase/reductase (SDR family) member 4 like 2	Phase I
DHRS7	dehydrogenase/reductase (SDR family) member 7	Phase I
DHRS7B	dehydrogenase/reductase (SDR family) member 7B	Phase I
DHRS7C	dehydrogenase/reductase (SDR family) member 7C	Phase I
DHRS9	dehydrogenase/reductase (SDR family) member 9	Phase I
DHRSX	dehydrogenase/reductase (SDR family) X-linked	Phase I
DPEP1	dipeptidase 1 (renal)	Phase I

Gene Symbol	Full Gene Name	Class
FMO6P	flavin containing monooxygenase 6	Phase I
HAGH	hydroxyacylglutathione hydrolase	Phase I
IAPP	islet amyloid polypeptide	Modifier
KCNJ11	potassium inwardly-rectifying channel, subfamily J, member 11	Modifier
LOC728667	similar to dehydrogenase/reductase (SDR family) member 2 isoform 1	Phase I
LOC731931	similar to dehydrogenase/reductase (SDR family) member 2 isoform 1	Phase I
MAT1A	methionine adenosyltransferase I, alpha	Modifier
METAP1	methionyl aminopeptidase 1	Phase I
PDE3A	phosphodiesterase 3A, cGMP-inhibited	Phase I
PDE3B	phosphodiesterase 3B, cGMP-inhibited	Phase I
PLGLB1	plasminogen-like B1	Phase I
ATP7A	ATPase, Cu++ transporting, alpha polypeptide (Menkes syndrome)	Modifier
ATP7B	ATPase, Cu++ transporting, beta polypeptide	Modifier
CFTR	cystic fibrosis transmembrane conductance regulator	Modifier

APPENDIX 6 DIAGNOSTIC CRITERIA FOR DRUG AND ALCOHOL ABUSE

The following is taken from DSM-IV:

Diagnostic Criteria for Psychoactive Substance Dependence

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

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

Criteria for Severity of Psychoactive Substance Dependence:

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

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

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

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

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

Diagnostic Criteria for Psychoactive Substance Abuse

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

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

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

[redacted]

[redacted]

[redacted]

[redacted]

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02

Section Number & Title	Description of Change	[redacted]
Title Page	Updated study director/medical monitor.	
2 Schedule of Activities (SOA)	Duplicate row for pregnancy test was deleted and the Day 8 pregnancy test was moved to Day 13 to 15/Study Discharge column and clarified for WOCBP only. Clarified vital signs, stool occult blood, whole blood for genotyping/ADME, and SAEs.	
2 SOA and 9.4.4 Clinical Safety Laboratory Assessments	Clarified urine dipstick for blood only if the participant is able to produce urine. Clarified that the pregnancy test is for WOCBP only.	
2 Schedule of Activities (SOA) 5.1 Overall Design	Updated the screening window from 21 days to 28 days.	
5.2 Number of Participants	Clarified the target sample size of 32 participants is to achieve 24 participants who complete the 4 study treatments.	

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	[redacted]
6.2 Exclusion Criteria	Clarify prior aspirin use to at least 1 week before dosing in exclusion criteria 2a. Updated duration contraceptive methods to be used for men in exclusion criteria 3e.	
7.7.1 Prohibited and/or Restricted Treatments	Clarify concomitant use of NSAIDS or aspirin to within 1 week prior to study drug administration. Also allow the use of topical antifungals.	
9.5 Pharmacokinetics	Extraction ratio was deleted	
9.7.1 Genotyping and ADME Sampling	Clarify that whole blood sample to be drawn at baseline for dosed participants.	
Appendix 4 WOCBP Definitions and Methods of Contraception	Requirements for WOCBP participants to use one highly effective and/or one less effective method of contraceptive has been added. Duration of contraceptive methods for males has been updated to align with updating exclusion criteria 3e.	
Title Page	Updated study director/medical monitor.	
2 Schedule of Activities (SOA)	Duplicate row for pregnancy test was deleted and the Day 8 pregnancy test was moved to Day 13 to 15/Study Discharge column and clarified for WOCBP only. Clarified vital signs, stool occult blood, whole blood for genotyping/ADME, and SAEs.	

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
2 SOA and 9.4.4 Clinical Safety Laboratory Assessments	Clarified urine dipstick for blood only if the participant is able to produce urine. Clarified that the pregnancy test is for WOCBP only.	Clarification added based on feedback from a site that many of the end stage renal disease patients (ESRD) are unable to produce urine.
2 Schedule of Activities (SOA) 5.1 Overall Design	Updated the screening window from 21 days to 28 days.	Being a hemodialysis patient study, flexible in the screening period is needed to schedule the study with the participant's hemodialysis schedule.
5.2 Number of Participants	Clarified the target sample size of 32 participants is to achieve 24 participants who complete the 4 study treatments.	It was not intended to achieve 24 evaluable participants as previously written which would be those who received 1 dose of study drug.
6.2 Exclusion Criteria	Clarify prior aspirin use to at least 1 week before dosing in exclusion criteria 2a. Updated duration contraceptive methods to be used for men in exclusion criteria 3e.	Updated based on review of screen failures and the change will not likely impact the study assessment or patient safety. Definitive embryo-fetal development (EFD) studies have been completed and findings from these studies indicate that BMS-986177 is non-terogenic and non-genotoxic.
7.7.1 Prohibited and/or Restricted Treatments	Clarify concomitant use of NSAIDS or aspirin to within 1 week prior to study drug administration. Also allow the use of topical antifungals.	Updated based on review of screen failures. These changes will not likely impact the study assessment or patient safety.
9.5 Pharmacokinetics	Extraction ratio was deleted	It was a duplication to %DR (Percent dose of BMS-986177 recovered in dialysate %).
9.7.1 Genotyping and ADME Sampling	Clarify that whole blood sample to be drawn at baseline for dosed participants.	To make this consistent with Section 2 Schedule of Activities (SOA).
Appendix 4 WOCBP Definitions and Methods of Contraception	Requirements for WOCBP participants to use one highly effective and/or one less effective method of contraceptive has been added. Duration of contraceptive	Appendix has been updated to reflect the latest protocol model template. Definitive embryo-fetal development (EFD) studies have been completed and findings from these studies indicate that BMS-986177 is non-terogenic and non-

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	methods for males has been updated to align with updating exclusion criteria 3e.	genotoxic.

[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01

Section Number & Title	Description of Change	[redacted]
Section 3.3: Benefit/Risk Assessment	Safety data was updated from FIH SAD/MAD study (CV010001). Also, the safety data from the HD PK study (CV010012) was added.	
Section 5.1: Overall Design	BMS dose 1 and BMS dose 2 were updated to be BMS-986177 100 mg and BMS-986177 300 mg, respectively. Other minor changes made in this section.	
Section 5.5: Justification for Dose	Updated targeted exposures based on hemodialysis PK study to support the BMS dose 1 (100 mg) and BMS dose 2 (300 mg)	
Section 6.2: Exclusion Criteria and Section 6.3: Lifestyle Restrictions	Exclusion criteria 1a, 1d, 1i, 1n, 3b, and 3e were clarified. Exclusion criterion 2b was added. Restrictions were updated.	
Section 7: Treatment	BMS-986177 100 mg and 300 mg (to replace BMS dose 1 and dose 2) were added to Table 7.-1 and Table 7.1-1.	
Section 7.2: Method of Treatment	Reference to IRT was removed.	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	[redacted]
Assignment and Section 7.3: Blinding		
Section 7.7.1: Prohibited and/or Restricted Treatments	Prohibited/restricted treatments were updated.	
Section 8.1: Discontinuation from Study Treatment	Updated the discontinuation criteria on events of complete clotting of hemodialysis circuit to include enoxaparin treatment arm and 5 or more patients.	
Section 9.5: Pharmacokinetics	Updates to further clarify Table 9.5-1 were made.	
Section 9.6: Pharmacodynamics	Updates to further clarify Table 9.6-1 and Table 9.6-2 were made.	
Section 9.8: Biomarker	Updates to further clarify Table 9.8-1 and Table 9.8-2 were made. Also, to remove clotting assessment from the blood line and URR. Kt/V assessment was further clarified.	
All	Minor formatting and typographical corrections. One additional reference was added. Additional abbreviations were added to Appendix 1.	

STUDY ACKNOWLEDGMENT/DISCLOSURE

I understand that this protocol contains information that is confidential and proprietary to Bristol-Myers Squibb Company (BMS). Any supplemental information that may be added to this document is also confidential and proprietary to BMS and must be kept in confidence in the same manner as the contents of this protocol.

I have read the original protocol/revised protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein and will make a reasonable effort to complete the study within the time designated.

I will provide copies of the protocol and access to all information furnished by BMS to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I will provide protocol information to my Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s]. I understand that original protocol/revised protocols 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.

I agree that the contents of the protocol may not be disclosed to any other person or entity or used for any other purpose without the prior written consent of BMS. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to BMS of any such disclosure.

I agree that the study data derived from this protocol may only be used and disclosed in furtherance of the protocol, for the medical treatment of a study subject or for publication of study results in accordance with the terms of the CTAg or as otherwise permitted by the terms of the CTAg.

I agree not to collect or use samples (e.g., tissue, blood, serum, urine) or collect data (other than for diagnostic or treatment purposes) from the study subjects while enrolled in the study, except as expressly permitted by the protocol or the terms of the CTAg.

I understand that I may terminate or suspend enrollment of the study at any time if it becomes necessary to protect the best interests of the study subjects. Unless otherwise provided in the CTAg, the study may be terminated at any time by BMS, with or without cause.

Original Protocol ☐ Revised Protocol ☒

Protocol Number: CV010010 Site Number: 0003

Date of Protocol: September 06, 2017

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Investigator Jolene Berg MD Date 21SEP2017
(signature)

Jolene Kay Berg, MD
(printed name*)