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Clinical Protocol CV013-034

A Randomized, Double-Blind, Placebo-Controlled, Cross-over Phase 2 Study of Continuous 8-Hour Intravenous Infusions of BMS-986231 in Patients with Heart Failure and Impaired Systolic Function Given a Standard Dose of Loop Diuretic

Study Director
Maria Borentain, MD

DOCUMENT HISTORY

Document	Date of Issue	Approver(s)	Summary of Change
Original Protocol	09-May-2018	[redacted]	Not applicable
Protocol v2.0	11-Jan-2019		Updates were made according to Protocol Amendment 1.0, which includes: • Update of the address for BMS • Update of the Medical Monitor • Update of Appendix 3 to clarify the definition of adverse event to be used in the study • Correction position vital signs in Table 1 In addition, minor editorial corrections were included
Protocol v3.0	14-Mar-2019		Updates were made according to Protocol Amendment 2.0, which include: • Allowance of more flexibility to the investigators regarding withholding diuretics and fluid intake and emphasizing that the target population should be patients with stable chronic heart failure with reduced ejection fraction (HFrEF) without signs of decompensation. • Clarification that if the end of infusion occurs prior to 8 hours after start of infusion (H8), the end of infusion should be considered an early discontinuation. • Minor editorial and administrative changes.

Protocol v4.0	15-Apr-2019	[redacted]	Updates were made according to Protocol Amendment 3.0, which include: • Changes to Section 5.1 Inclusion Criteria, to allow patients with lower levels of baseline natriuretic peptides and higher baseline estimated glomerular filtration rate (eGFR). • Minor editorial or administrative changes or corrections of typographical errors.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Cross-over Phase 2 Study of Continuous 8-Hour Intravenous Infusions of BMS-986231 in Patients with Heart Failure and Impaired Systolic Function Given a Standard Dose of Loop Diuretic

Study Phase: 2

[redacted]

[redacted]

Study Population:

Study participants will be stable chronic patients with HFrEF, left ventricular EF ≤ 45%, treated with chronic guideline-directed therapy for HF including chronic loop diuretics, angiotensin-converting-enzyme inhibitor (ACEi), angiotensin-receptor blockers (ARB), mineralocorticoid receptor antagonists (MRAs), angiotensin-receptor/neprilysin inhibitor (ARNI) or / and β-blockers as tolerated.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• Evaluate the effects of HNO donor BMS-986231 on 4-hour urine output in patients with HFrEF after administration of 40 mg of IV furosemide	• 4-hour urinary output following intravenous administration of 40 mg furosemide to HFrEF patients receiving BMS-986231 infusion compared to placebo
Secondary	
• Assess the effect of BMS-986231 on fractional excretion of Na (FeNa)	• FeNa in patients with HFrEF while on BMS-986231 compared to placebo
• Assess the effect of BMS-986231 on fractional excretion of K (FeK)	• FeK in patients with HFrEF while on BMS-986231 compared to placebo

Objectives	Endpoints
• Assess the effects of BMS-986231 on furosemide urinary and plasma concentration and the ratio urinary sodium to urinary furosemide	• Furosemide urinary and plasma concentration in patients with HFrEF while on BMS-986231 compared to placebo • Ratio Urinary Na to Urinary furosemide after BMS-986231 compared to placebo
Safety	
• Assess safety of BMS-986231	• Clinically relevant hypotension during infusion, adverse events, clinical laboratory values, vital signs, ECGs, telemetry, physical examinations
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Objectives	Endpoints
	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Design:

This is a double blinded, randomized, two-way cross-over, placebo-controlled study to evaluate the effects of HNO donor BMS-986231 on 4-hour urine output in stable chronic HFrEF patients after administration of 40 mg of IV furosemide. The study consists of 2 one-day treatment periods (BMS-986231 or placebo) separated by a washout period of at least 7 days (Day 2 to at least Day 8), but no more than 4 weeks. Each period includes 8-hour infusion. A standard dose of 40 mg IV furosemide will be administered by IV bolus injection at the midpoint (4 hour, H4) of an 8-hour infusion. Screening for inclusion in the study will be performed up to 4 weeks before the first treatment day (Day 1 of the first period). Approximately 20 eligible subjects will be randomized. For each period, subjects must remain for at least 3.5 hours after the end of infusion. Patients may stay overnight or may be discharged the same day 3.5 hours after end of infusion if certain conditions are met (see Section 4.1 for details). The total duration of the study will be approximately 8 weeks.

Number of Participants:

This study will include approximately 20 participants.

Treatment Arms and Duration:

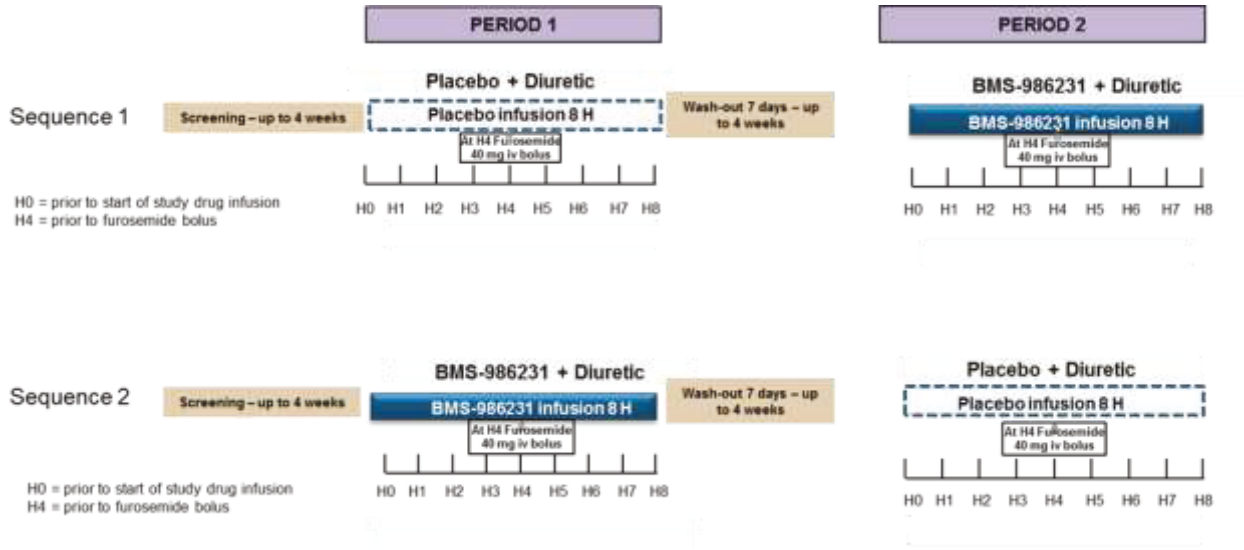
Study treatment: BMS-986231 or placebo will be administered in a blinded manner for 8 hours as continuous IV infusion. BMS-986231 will be administered at the dose of 12 µg/kg/min, corresponding to an infusion rate of 20 mL/H. Placebo will be an infusion of D5W that will be administered at the flow rate of 20 mL/H.

At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide will be administered through a separate IV line, given slowly over 1-2 minutes.

In case of significant decrease in systolic blood pressure at any time during the infusion, an algorithm will be used to down-titrate / interrupt or discontinue the study drug infusion (see Section 6.4 in the protocol).

Study Drug for CV013-034		
Medication	**Potency**	**IP/Non-IMP**
BMS-986231	240 mg/vial	IP
Placebo	Not Applicable	IP
Furosemide	10 mg/mL	Non-IMP

1.2 Schema



1.3 Schedule of Activities (SOA)

Schedule of assessments is described in Table 1 (screening) and Table 2 (during study), for pharmacokinetic (PK) sampling schedule see Table 7, for urine collection intervals for urine output and PK see Table 8, [redacted]

For PK, H0 (pre-dose, before start of infusion) samples for BMS-986231 and furosemide will be obtained within 30 minutes before start of the infusion. Postdose samples will be obtained in time margins of ±15 minutes.

For safety and exploratory assessments, H0 (pre-dose, before start of infusion) assessments will be performed within 1 hour prior to dosing. Safety assessments and exploratory assessments postdose will be performed with time margins of ±15 minutes of the nominal time points.

For urine sampling, pre-dose (before start of infusion) sampling will be started within 1 hour prior to dosing. Urine sample intervals postdose will be performed with time margins of ±15 minutes of the nominal time points. The 4.0 hours urine sample interval will be obtained within 15 minutes before furosemide bolus. The 8.0 hours urine sample interval will be obtained within 15 minutes before end of infusion.

The actual time points of PK, exploratory and safety laboratory collection will be documented in the electronic case report form (eCRF).

In the event assessments are planned for the same scheme time, the following sequence should be followed:

(1) vital signs assessments including body temperature;

(2) electrocardiogram (ECG) recording;

(3) blood sampling.

Table 1: Screening Procedural Outline (CV013-034)

Procedure	Screening Visit	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	
[redacted]	[redacted]	
Safety Assessments		
Physical Examination	X	If the screening physical examination is performed within 3 days prior to first dosing then a single exam may count as both the screening and pre-dose evaluation. Includes height, weight, and BMI.
Vital Signs	X	Includes body temperature, respiratory rate, and supine 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.
Adverse Events Assessment	X	SAEs must be collected from the date of the participant's Informed consent.
ECG	X	ECGs should be recorded after the participant has been supine for at least 5 minutes. At screening, single ECGs will be recorded.
Laboratory Tests	X	Includes blood (hematology, serum chemistry, NT-proBNP or BNP [details in the protocol section]) and urine samples. Participants are required to fast for at least 10 hours prior to the collection of specimens for clinical laboratory tests (details in the protocol Section 8.4.6).
Pregnancy Test	X	For WOCBP only.

Table 2: On Treatment Procedural Outline (CV013-034)

Procedure	Treatment Period			Notes
	Period 1 Day 1	Washout (7-28 days)	Period 2 Day 1	Washout between periods should be at least 7 days and no more than 4 weeks.
Safety Assessments				
Weight	X		X	Weight within 15 minutes prior to and within 15 minutes after the end of the infusion[a] in each treatment period with bio-impedance scale. Weight should be measured after the void.
Targeted physical examination	X		X	To be done at H0 (before start of infusion). Based on subject's report since the last visit. Includes temperature, signs and symptoms of congestion. If the screening physical examination is performed within 3 days prior to first dosing then a single physical exam may count as both the screening and at H0 (before start of infusion) evaluation.
Vital Signs (Blood pressure and heart rate)	X		X	Prior to infusion, and 30 minutes for first hour then every 1 hour until discontinuation of infusion, then at H9, H10 and H11.5 (3.5 hour after end of infusion[a]) in each treatment period.
Peripheral Oxygen Saturation	X		X	Prior to the start of infusion and immediately prior to the end of the infusion[a] in each treatment period, measured with a pulse oximeter device.
12-lead ECG	X		X	Prior to the infusion and after end of infusion[a] (both with 15 minutes window) in each treatment period. Triplicate ECGs will be recorded.
Telemetry	X		X	From start of infusion to 3 hours after end of infusion[a] in each treatment period.
Adverse Events Assessment	X		X	Nonserious AEs will be collected from the start of the study drug infusion until 24 hours after end of infusion[a] in each treatment period of dosing. Serious adverse events must be collected from the date of Informed consent and will be assessed up to 30 days after end of infusion[a] of the last period.
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2: On Treatment Procedural Outline (CV013-034)

Procedure	Treatment Period			Notes
	Period 1 Day 1	Washout (7-28 days)	Period 2 Day 1	Washout between periods should be at least 7 days and no more than 4 weeks.
Follow-up call/assessment	X		X	To be done at Day 2 of each period. Will inquire about general status and occurrence of any AEs. For each period, subjects must remain for at least 3.5 hours after the end of infusion[a]. Patients may stay overnight or may be discharged the same day 3.5 hours after end of infusion[a] if certain conditions are met (see Section 4.1 for details)
Laboratory Tests				
Hematology and Serum Chemistry	X		X	Laboratory tests will be performed in the morning of each treatment day (H0 [before start of infusion], H4 [just before furosemide bolus], and H8). See protocol Section 8.4.6 for details.
Pregnancy Test (WOCBP only)	X		X	
Blood sampling for PK (furosemide and BMS-986231 [and its metabolites])	X		X	Blood sampling for PK will be done at H0 (before start of infusion), H2 and at H4 hours (just before furosemide bolus), H5, H6, H8 (or end of infusion[a]) and H10 (2 hours after the end of the infusion[a]) in each treatment period. In addition, PK samples should be taken when the dose is lowered or discontinued (see protocol Section 8.5).
Blood sampling for Na, K, bicarbonate, creatinine, and eGFR	X		X	Blood sampling for Na, K, bicarbonate, creatinine, and eGFR will be done at H0 (before start of infusion), H4 (just before furosemide bolus), H5, H6, H7, H8 (or end of infusion[a]) in each treatment period.
Urine sampling for furosemide and BMS-986231 (or its metabolites)	X		X	Urine samples can be taken from the urine collection intervals done for the urinary output (see Table 8 in Section 8.5.1). An aliquot for both sets of metabolites and a back-up will be required for the analysis.
Urine sampling for Na, K, P, Cl, creatinine and bicarbonate concentrations	X		X	Urine samples can be taken from the urine collection intervals done for the urinary output (see Table 8 in Section 8.5.1).

Table 2: On Treatment Procedural Outline (CV013-034)

Procedure	Treatment Period			Notes
	Period 1 Day 1	**Washout (7-28 days)**	**Period 2 Day 1**	**Washout between periods should be at least 7 days and no more than 4 weeks.**
Efficacy Assessments				
Urinary output	X		X	Prior to start of infusion, patients will be asked to void and urine collected. A bladder scan (ultrasound) can be performed to ensure adequate bladder emptying. Patients will be asked to void at least every 2 hours during the first 4 hours post-start infusion and before furosemide bolus, and at least hourly from 4 to 8 hours post-start infusion. A second bladder scan can be performed at H8 (8 hours after start of infusion and just after study drug discontinuation and after the void). A final void will be done at 2 hours after the study drug discontinuation[a]. The urine will be collected and volume recorded for each collection interval.
Whole body bio-impedance				Prior to start of study drug infusion, at H4 (4 hours after the start of infusion and prior to furosemide bolus), at H8 (8 hours after the start of infusion and prior to study drug discontinuation), H10 (2 hours after the end of the infusion[a]) in each treatment period.
Echocardiography	X		X	Prior to start of study drug infusion, at H4 (4 hours after the start of infusion and prior to before furosemide bolus), at H5, H6, H8, and H10 (2 hours after the end of the infusion[a] in each treatment period).
Lung ultrasound	X		X	Prior to start of study drug infusion, at H4 (4 hours after the start of infusion and before furosemide bolus) and at H8 (end of infusion[a]).
Clinical Drug Supplies				
Randomize	X			Subjects will be randomized prior to start of infusion. Subjects will be randomized 1:1 to either BMS-986231 or Placebo in Period 1 and to either placebo or BMS-986231 in Period 2, such that within a sequence each patient will receive in random order one infusion of placebo.
Administration of Study Drug	X		X	
Administration of furosemide bolus	X		X	Furosemide bolus administration at H4 (4 hours after start of infusion of BMS-986231 or Placebo).

Table 2: On Treatment Procedural Outline (CV013-034)

Procedure	Treatment Period			Notes
	Period 1 Day 1	Washout (7-28 days)	Period 2 Day 1	Washout between periods should be at least 7 days and no more than 4 weeks.
[redacted]				
[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]

[a] If end of infusion occurs prior to 8 hours after start of infusion (H8), the end of infusion should be considered early discontinuation. In case of an early discontinuation, the timing for the assessments will be adapted accordingly, ie, H8 will be immediately after end of infusion, H9 will be 1 hour after end of infusion, H10 will be 2 hours after end of infusion, H11 will be 3 hours after end of infusion, and H11.5 will be 3.5 hours after end of infusion, as applicable.

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 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 clinical trial agreement or as otherwise permitted by the terms of the clinical trial agreement.

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 clinical trial agreement.

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 clinical trial agreement, the study may be terminated at any time by BMS, with or without cause.

Original Protocol: ☐ Revised Protocol: ☒

Protocol Number: CV013-034 Site Number:

Date of Protocol or Revised Protocol: 15-Apr-2019

IND Number: NA EUDRACT Number: 2018-000970-31

Investigator: Date:

(signature)

(printed name)

2 INTRODUCTION

Heart failure (HF) is a leading cause of morbidity and mortality. Acute decompensated heart failure (ADHF) is the number one cause of hospitalization in the elderly, and is associated with considerable morbidity, mortality and economic cost.[1,8,9,10,11] Although advances in drug and device treatment of chronic HF over the past 40 years have led to improvements in outcome of these patients, the morbidity and mortality of HF remains high. In contrast, there have been few advances in the approach to treat episodes of ADHF over the same time period, and no therapies have been demonstrated to improve long- term clinical outcomes.[12]

Standard of care therapies for ADHF are based on the use of intravenous (IV) diuretics to promote fluid removal to reduce dyspnea, and in some patients, oral or IV vasodilators, to reduce the load on the heart and improve cardiac performance. Collectively, these treatments may reduce dyspnea but do not target the primary cause of HF, impaired cardiac contractility. Drugs that specifically enhance diminished cardiac contractility, called inotropic agents, may have an important role to help rapidly improve hemodynamics leading to rapid symptom relief. However the use of currently available cardiac inotropic drugs is associated with increased heart rate and myocardial oxygen consumption, induction of atrial and ventricular arrhythmias, concerns about provocation of ischemia, and adverse long-term outcomes, limiting the use of these inotropic agents to low cardiac output state with signs of end-organ hypoperfusion.[13,14,15]

An agent that increases contractility, while avoiding the adverse safety profile of an inotropic agent and retaining the capacity to unload the heart, could address a significant unmet medical need and be used in a broader patient population.

In this context, BMS-986231, a second generation HNO donor, is being developed in ADHF. It has demonstrated vasodilation, enhanced inotropy and improved relaxation in animal models and improved hemodynamics consistent with vasodilation and inotropic effect in early studies in humans.

Heart failure continues to be a leading cause of morbidity and mortality in the developed world. In the United States alone, an estimated 5.7 million people have HF, contributing to approximately 1 million hospital admissions and 280,000 deaths annually. In patients with ADHF, standard therapies are targeted at fluid removal (via diuretics) and reduction of cardiac preload and afterload (via vasodilators). In addition to diuretics and vasodilators, the use of parenteral inotropes to improve cardiac contractility more directly is warranted in a subset of patients. Administration of conventional inotropic agents requires close monitoring in the hospital's intensive care unit setting due to potential safety risks such as tachyarrhythmia and hypotension, and is also associated with increased myocardial oxygen consumption and longer-term adverse outcomes. Therefore, there is a need for a safe and effective therapy that would reduce cardiac loads in the clinical setting of ADHF, while safely enhancing cardiac output through improvement of diastolic and systolic function.

HNO (nitroxyl, nitrosyl hydride, or hydrogen oxonitrate) is a compound closely related to NO (nitric oxide). However, their physiological effects and biological mechanisms of action are distinct. The biological effects of HNO are reversible and thought to be mediated by direct reaction

with thiolates in myocardial and vascular target proteins in an O_2-independent manner.[1,2,3,4] In animal models of HF, HNO reduces both preload and afterload and enhances the relaxation and contractility of the failing heart.[5,6] Vasodilation by HNO appears to be mediated at least in part by soluble guanylate cyclase. In cardiomyocytes, HNO modifies both the ryanodine receptor and the cardiac sarcoplasmic reticulum calcium adenosine triphosphatase (SERCA)/phospholamban to increase the efficiency of calcium cycling without a concomitant increase in overall cellular calcium levels. In addition, HNO donors do not increase heart rate (HR) or myocardial oxygen consumption (MVO_2).[7] HNO cannot be administered directly and must be delivered as a prodrug (ie, an HNO donor). Suitable bioanalytical methods for measuring concentrations of HNO in biologic samples do not exist; therefore, characterization of the prodrug and metabolites serves as the primary means of understanding HNO disposition.

BMS-986231 is a pH-sensitive prodrug of HNO that is being developed for IV administration for the treatment of ADHF. Following IV administration, BMS-986231 nonenzymatically releases the active pharmacophore, HNO, and an inactive sulfinic acid byproduct that is designated BMT 284730.

Preclinical in vivo studies show that infusion of BMS-986231 produces consistent cardiovascular (CV) effects in several models, with a minimum effective dose of 0.7 µg/kg/min. These effects include peripheral vasodilation, increased inotropy, and improved lusitropy; they persist for the duration of infusion and partially resolve within 60 minutes after the end of infusion. The CV effects are evident in both normal and failing myocardium and occur without evidence of direct chronotropy or increased myocardial oxygen demand. BMS-986231 has demonstrated favorable hemodynamic effects in patients with advanced HF, including reductions in right and left ventricular filling pressures and increase in cardiac index. The salient features of the compound are further described below.

A detailed description of the chemistry, pharmacology, efficacy, and safety of BMS-986231 is provided in the Investigator's Brochure (IB).[16]

[redacted]

[redacted]

3 OBJECTIVES AND ENDPOINTS

Table 3: Objectives and Endpoints

Objectives	Endpoints
Primary	
• Evaluate the effects of HNO donor BMS-986231 on 4-hour urine output in patients with HFrEF after administration of 40 mg of IV furosemide	• 4-hour urinary output following intravenous administration of 40 mg furosemide to HFrEF patients receiving BMS-986231 infusion compared to placebo
Secondary	
• Assess the effect of BMS-986231 on fractional excretion of Na (FeNa)	• FeNa in patients with HFrEF while on BMS-986231 compared to placebo
• Assess the effect of BMS-986231 on fractional excretion of K (FeK)	• FeK in patients with HFrEF while on BMS-986231 compared to placebo
• Assess the effects of BMS-986231 on furosemide urinary and plasma concentration and the ratio urinary sodium to urinary furosemide	• Furosemide urinary and plasma concentration in patients with HFrEF while on BMS-986231 compared to placebo • Ratio Urinary Na to Urinary furosemide after BMS-986231 compared to placebo
Safety	
• Assess safety of BMS-986231	• Clinically relevant hypotension during infusion, AEs, clinical laboratory values,

Table 3: Objectives and Endpoints

Objectives	Endpoints
	vital signs, ECGs, telemetry, physical examinations
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table 3: Objectives and Endpoints

Objectives	Endpoints
• [redacted]	[redacted]

4 STUDY DESIGN

4.1 Overall Design

This is a double blinded, randomized, two-way cross-over, placebo-controlled study to evaluate the effects of HNO donor BMS-986231 on 4-hour urine output in stable chronic HFrEF patients after administration of 40 mg of IV furosemide. The study consists of 2 one-day treatment periods (BMS-986231 or placebo) separated by a washout period of at least 7 days (Day 2 to at least Day 8), but no more than 4 weeks. Each period includes 8-hour infusion. A standard dose of 40 mg IV furosemide will be administered by IV bolus injection at the midpoint (4 hour, H4) of an 8-hour infusion. Screening for inclusion in the study will be performed up to 4 weeks before the first treatment day (Day 1 of the first period). Approximately 20 eligible subjects will be randomized. For each period, subjects must remain for at least 3.5 hours after the end of infusion. Patients may stay overnight or may be discharged the same day 3.5 hours after end of infusion if certain conditions are met (see Section 4.1). The total duration of the study will be approximately 8 weeks.

Study Drug

BMS-986231 or placebo will be administered in a blinded manner for 8 hours as continuous IV infusion. BMS-986231 will be administered at the dose of 12 µg/kg/min, corresponding to an infusion rate of 20 mL/H. Placebo will be an infusion of D5W that will be administered at the flow rate of 20 mL/H.

At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide will be administered through a separate IV line, given slowly over 1 to 2 minutes.

In case of significant decrease in SBP at any time during the infusion, an algorithm will be used to down-titrate / interrupt or discontinue the study drug infusion (see Section 6.4 in the protocol).

Screening

Screening for inclusion in the study will be performed up to 4 weeks before the first treatment day. Screening will assess the eligibility criteria. After screening, study participants will be enrolled in the study according to their eligibility as per the inclusion and exclusion criteria, and will be randomized to 1 of the 2 sequences that will be conducted in parallel.

Treatment Day (Day 1 of Each Period)

Study participants will be admitted to the study facility the day before or on the treatment day, according to local practice and patient preferences. Assessment of symptoms and signs of HF, including body weight, vital signs and laboratory tests will be performed pre-dose (before start of infusion). On each treatment day, blood pressure and HR should be within the inclusion / exclusion criteria limits prior to study drug administration. The study drug infusion could start without waiting for the results of the laboratory assessments done in the morning of the treatment day at the study facility if the following criteria are met:

- The results of the laboratory assessment at screening / previous period are within ranges compatible with inclusion criteria,
- The study participant was medically stable with no signs of overt HF decompensation or deteriorating signs and symptoms of congestion and without change in medication since the screening visit / previous period.

If the laboratory tests (e.g. electrolytes, serum creatinine, estimated glomerular filtration rate (eGFR), hemoglobin, transaminases) on the morning prior to infusion, are not within inclusion and exclusion criteria limits, the study drug could be interrupted / discontinued after consultation with the Medical Monitor. The abnormalities should be corrected before the next treatment period.

Physical examinations, vital sign measurements, 12-lead ECG and urinary output will be performed at selected times throughout the dosing interval. Participants will be closely monitored for AEs throughout the study. Blood samples will also be collected at selected intervals after start of study drug administration for PK analysis and biomarkers.

Prior to start of the infusion, study participants will be asked to void and urine collected. A bladder scan can be performed to ensure adequate bladder emptying. Patients will be asked to void at least every 2 hours during the first 4 hours post-start infusion and before furosemide bolus, and at least hourly from 4 to 8 hours post-start infusion. At 8 hours after start of study drug infusion, just before study drug discontinuation, a void will be done, collected and recorded and a second bladder ultrasound can be performed to ensure adequate bladder emptying. Urine will be collected until 2 hours after the study drug discontinuation.

Discharge

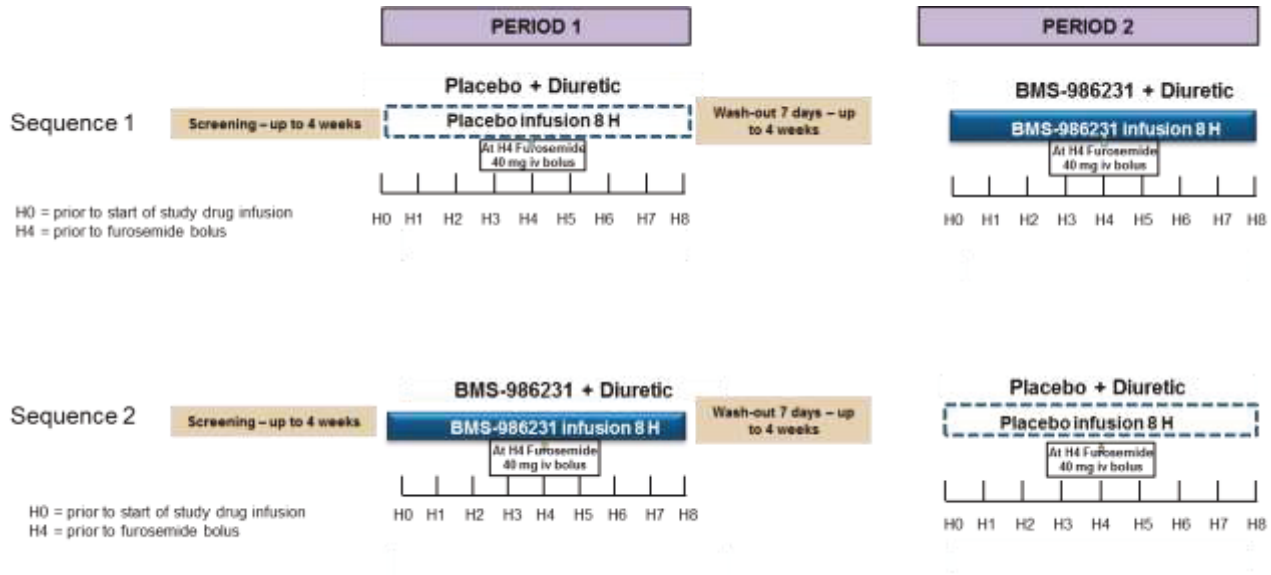
Study participants may remain overnight at the study facility. There is the possibility to discharge the patients the same day if the following conditions are met:

- Study participants have been under medical supervision for approximately 3.5 hours post-dose
- In the opinion of the investigator an overnight stay is not warranted
- There is no hypotension or other events of concern after mobilization
- None of the following events occurred during the study drug infusion: prolonged hypotension, symptoms of hypotension, new onset of sustained arrhythmia requiring

pharmacologic or other interventions, any other events of concern e.g. chest pain suggestive of ischemia.

The study design schematic is presented in Figure 1.

Figure 1: Study Design Schematic



4.1.1 Data Monitoring Committee and Other External Committees

There is no Data Monitoring Committee (DMC) planned for this study. Occurrence of significant safety events will be submitted for review to the independent DMC that monitors the ongoing Phase 2b study, evaluating the safety, tolerability and effectiveness of BMS-986231 in a population of acute decompensated HF patients ([redacted].

4.2 Number of Participants

The number of subjects to be enrolled was chosen based on practical considerations. Approximately 20 HFrEF patients will be randomized to one of two sequences: BMS-986231/diuretic followed by placebo/diuretic or placebo/diuretic followed by BMS-986231/diuretic.

Further details are provided in Section 9.1.

4.3 End of Study Definition

The start of the trial is defined as the first visit for the first participant screened. End of trial is defined as the last visit or scheduled procedure shown in Section 1.3, 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.

5 STUDY POPULATION

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

5.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Subjects will be required to provide a written informed consent.

2) Type of Participant and Target Disease Characteristics

a) Males and Females, ages 18 or age of majority or older.

b) Left ventricular EF <45%, as assessed by echocardiography, a multigated acquisition (MUGA) scan or magnetic resonance imaging (MRI) scan within 18 months.

c) On stable chronic guideline-directed therapy for HF including chronic loop diuretics, ACEi, ARBs, MRAs, ARNI or / and β-blockers as tolerated, with no changes of these medications in the past 2 weeks.

d) Not applicable per Protocol Amendment 3.0.

e) Not applicable per Protocol Amendment 3.0.

f) Not applicable per Protocol Amendment 3.0.

g) Elevated natriuretic peptides (N terminal-pro BNP [NT-proBNP] ≥ 200 pg/mL or brain natriuretic peptide [BNP] ≥ 60 pg/mL). For subjects with atrial fibrillation, NT-pro BNP ≥ 400 pg/mL or BNP ≥ 120 pg/mL.

h) eGFR between 30 and 80 mL/min/1.73m^2.

3) Age and Reproductive Status

a) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 24 hours prior to the start of each study treatment.

b) Women must not be breastfeeding.

c) WOCBP must agree to follow instructions for methods of highly effective contraception (APPENDIX 4) for 31 days after discontinuation (duration of study drug exposure plus 30 days duration of one ovulatory cycle).

d) Males who are sexually active with WOCBP must require these partners to follow instructions for highly effective methods of contraception (APPENDIX 4) for 91 days after discontinuation (duration of study drug plus 90 days (duration of sperm turnover).

e) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, but 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.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1) Target Disease Exceptions

a) SBP < 115 mm Hg or > 180 mm Hg at screening or pre-randomization.

b) Heart rate < 50 beats per minute (bpm) or > 120 bpm at screening or pre-randomization.

c) Primary HF etiology attributable to either restrictive/obstructive cardiomyopathy, idiopathic hypertrophic or uncorrected severe valvular disease as defined by American Heart Association (AHA)/American College of Cardiology (ACC)/European Society of Cardiology (ESC) criteria.

d) Patients with urinary/prostate disorders with urinary retention/significant bladder dysfunction or urinary incontinence.

e) Inability to comply with the serial urine collection procedures.

f) Pericardial tamponade or constrictive pericarditis.

g) Left ventricular (LV) assist device or prior heart transplant.

h) Hospitalized for acute decompensated HF in the previous month.

i) New York Heart Association (NYHA) Class IV symptoms of HF.

j) Hospitalized with acute coronary syndrome, coronary revascularization or acute myocardial infarction during the previous 90 days prior to screening.

k) Have a history of a cerebral vascular accident (cerebrovascular accident [CVA] or stroke) or of a transient ischemic attack (TIA) during the previous 90 days prior to screening.

l) Considered clinically unstable for any condition.

m) Serious comorbid non-cardiovascular disease in which the life expectancy of the subject is < 3 months.

n) Liver disease defined as history of cirrhosis with evidence of portal hypertension such as varices, or encephalopathy, or total bilirubin > 3 mg/dL (> 34.2 μmol/L) or significant elevation of liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT] > 3 times the upper limit of normal).

o) Prior solid organ transplant.

2) Prior/Concomitant Therapy

a) Patients taking thiazides / metolazone or potassium-sparing diuretics (with the exception of spironolactone or eplerenone at doses ≤ 50 mg/day which are allowed).

3) Physical and Laboratory Test Findings

a) Have persistent abnormal serum electrolytes not resolved between screening and start of the study drug infusion, as defined by any of the following:

i) A sodium (Na+) concentration < 130 or > 145 mEq/L (mmol/L).

ii) A potassium (K+) concentration < 3.2 or > 5.5 mEq/L (mmol/L).

b) Have severe anemia, as documented by a hemoglobin < 9 g/dL (< 5.59 mmol/L).

4) Allergies and Adverse Drug Reaction

a) Any history of allergic reaction to components of BMS-986231, Captisol® or potassium acetate.

b) Any history of allergic reactions to furosemide.

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's approval is required).

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

c) Participation in an investigational clinical drug study within 30 days or 5 elimination half-lives, (whichever is longer) prior to randomization.

d) Prior participation and treatment in a study using BMS-986231.

e) Alcohol beverage consumption within 6 hours prior to randomization.

f) Body weight < 45 kg or ≥ 140 kg.

g) Site personel and their families.

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.

5.3 Lifestyle Restrictions

5.3.1 Meals and Dietary Restrictions

Study participants will be asked to eat their usual diet, but it should remain similar for the 3 days prior to the infusion. Patients should keep a 3-day diet diary to record what they consume. During the infusion, study participants will be given up to 200 mL / hour as fluid intake, as tolerated. Urinary output will be collected every 2 hours in the first 4 hours and then hourly from 4 hours to 8 hours after start of infusion.

On each treatment day standardized meals and snacks will be served. No fasting is required the evening prior to each treatment day.

5.3.2 Caffeine, Alcohol and Tobacco

Study participants will avoid alcohol in the 6 hours prior to infusion start and caffeine in the 12 hours prior to infusion start and during the stay in the clinic. Smoking is not allowed during the stay in the clinic.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. 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.

5.4.1 Retesting During Screening or Lead-In Period

Participant Re-enrollment: This study permits the re-enrollment of a participant that did not initially meet Inclusion/Exclusion criteria (i.e., participant has not been randomized). If re-enrolled, the participant must be re-consented.

Laboratory parameters and/or assessments that are included in Table 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 could allow for the patient to be randomized.

6 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:

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.

In this study the investigational products are BMS-986231 for injection and placebo.

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

In this study, the required potassium acetate used as a buffer for BMS-986231 infusions and furosemide are considered non-investigational products.

Study medication will be prepared by an unblinded pharmacist (or appropriate designee) on Day 1 of each period (treatment day), at time of randomization in the first period and before start of the infusion for the second period. Detailed instructions for preparing, reconstituting, and handling of BMS-986231 and placebo, as well as infusion setups, instructions for labeling individual infusion bags after they are prepared, and information on dosing solution stability are provided in the Study Pharmacy Manual.

Table 4: Study Treatments for CV013-034

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-986231 For Injection[a]	240 mg/vial	IP	Blinded	Vial(s) in a carton	Refer to the label on container and/or pharmacy manual
Furosemide	10 mg/mL	Non-IMP	Open Label	TBD	Refer to the label on container and/or pharmacy manual
Placebo	Not Applicable	IP	Blinded	TBD	Refer to the label on container and/or pharmacy manual
Potassium Acetate Injection, USP[b]	2 mEq/mL	Non-IMP	Open Label	Vial(s) in a carton.	Refer to the label on container or package insert / summary of product characteristics

[a] BMS-986231 for infusion contains active pharmaceutical ingredient BMS-986231 240 mg/vial formulated with Captisol® 3405 mg/vial

[b] Potassium Acetate Injection may be supplied by BMS centrally (ex-US sites) or through site sourcing procedures. It is used as a buffer for BMS-986231 infusion (1 mEq potassium per 100 mL of reconstituted BMS-986231 further diluted for infusion).

6.1 Treatments Administered

The selection and timing of dose for each participant is as follows:

Table 5: Selection and Timing of Dose

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
BMS-986231	12 µg/kg/min for 8 hours (20 mL/H)	Single infusion	IV
Placebo*	20 mL/H for 8 hours	Single infusion	IV
Furosemide	40 mg	Single IV bolus	IV

* Placebo will be a solution of 5% dextrose (D5W) that will be locally supplied by the site.

Restrictions related to food and fluid intake are described in Section 5.3.

6.2 Method of Treatment Assignment

All subjects who sign informed consent and are enrolled (including those not subsequently randomized or treated) will be assigned sequential subject numbers. Eligible subjects will be randomized according to a computer-generated randomization scheme.

If a potential subject is rescreened, a new identification number will be used.

Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with 00001, (e.g., 00001, 00002, 00003.... 00020). Those enrolled participants meeting inclusion and exclusion criteria will be eligible to be randomized. Randomization numbers will be assigned prior to dosing. Subjects who are re-enrolled (See Section 5.4) will be assigned a new participant number.

Participants will not be replaced if they are discontinued from the study.

6.3 Blinding

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

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

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

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

In case of an emergency, the investigator may open the emergency unblinding envelope to reveal the identity of the study drug for that participant. If such unblinding occurs, the investigator shall notify the Medical Monitor immediately. This information, including the reason for the blind being broken, must be recorded on the appropriate study status page of the Case Report Form (CRF). In addition, the information that is requested on the emergency unblinding envelope must be completed.

Randomization schedules will be shipped directly to a pharmacist or other individual(s) who will be responsible for the dispensing of blinded study drug. This (these) individual(s) will be unblinded to study drug identification but will not be involved in any other aspect of study conduct. The randomization schedules will be maintained in a secure location with access limited to authorized personnel.

6.3.1 Other Blinding and Unblinding

The Bioanalytical Sciences section or its designate may be unblinded to the randomized treatment assignments, in order to minimize unnecessary assays of samples from subjects during the placebo treatment period. Likewise, the Metabolism and Pharmacokinetics section or its designate may be unblinded, if metabolite profiling work is conducted.

In certain circumstances, a pharmacokineticist or designate(s) in Clinical Pharmacology and Pharmacometrics, biostatistician(s) and programmer(s) at BMS, or designee, may be unblinded in order to prepare preliminary summaries of PK and safety data, as needed. These summaries will not reveal individual subjects' treatment sequence assignments.

6.4 Dosage Modification

BMS-986231 or placebo

The administration of the study drugs will be done through an infusion pump connected to a single peripheral IV line. After priming the infusion set tubing and connecting the lines to the IV catheter, the pump should be set to deliver the rates of infusion indicated on the infusion bag label.

The pump infusion volume display should be re-set to 0 after priming the infusion line and just prior to the start of the infusion, and the total volume infused at the conclusion of the infusion after 8 hours, or at the time of any early discontinuation, should be recorded in the clinic source documents.

At any time during the administration of study drug, the study drug infusion must be discontinued if an AE or any other safety issue suggests it is not in the patient's best interest to continue to receive study drug.

The investigator has the option to adjust the study drug dosage level downward by 50%, interrupt or discontinue the study drug infusion in patients that develop hypotension, or if the patient experiences symptomatic hypotension that is not easily tolerated, as follows (and shown in Figure 2):

- **Study drug reduction**: Study drug is decreased by 50% if SBP decreases to levels <90 mmHg but ≥80 mmHg. The dose cannot be subsequently increased.
- **Study drug interruption**: Study drug is interrupted for 1 hour if SBP <80 mmHg or symptoms of low blood pressure occur. If the SBP is ≥ 105 mmHg after one hour interruption, the study drug could be resumed at 50 % of the dose.
- **Study drug discontinuation**: Study drug will be permanently discontinued if SBP remains < 105 mmHg after 1 hour interruption or if SBP decreases to levels <80 mmHg or symptoms of low blood pressure occur.

After a dose reduction, the dose cannot be increased again. Study drug will be permanently discontinued after it has been down titrated once, and criteria for dose reduction or interruption has been met again.

If an infusion in a given period is discontinued, patients remain eligible to complete the subsequent period.

Any decision to lower the dosage level of study drug or discontinue study drug should be based on the investigator's assessment of the patient's overall clinical stability, in the context of appropriate ongoing monitoring of the patient's condition.

A 50% dosage adjustment downward will be achieved by decreasing the rate of study drug infusion from 20 mL/H to 10 mL/H.

Furosemide will be administered through an IV bolus injection at H4 of study drug infusion. In the event the study drug has been reduced, furosemide injection is administered at H4 as planned. If the study drug has been temporarily interrupted, then restarted, furosemide will be administered after at least 4 hours of effective study drug infusion.

6.5 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.

Please refer to Pharmacy Manual for additional guidance on storage of study drug. Study drug not supplied by BMS will be stored in accordance with the package insert. Please refer to APPENDIX 2 for guidance on IP records and documentation.

Once study medication is reconstituted by the unblinded pharmacist, it will remain stable at room temperature for a maximum of 8 hours. Reconstituted study medication must be refrigerated immediately if dosing will not start within 1 hour.

It is recommended that study medication be removed from the refrigerator and left at room temperature for approximately 30 minutes prior to the start of the infusion.

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).

Storage facilities for controlled substances must be securely locked and substantially constructed, with restricted access to prevent theft or diversion, as applicable by local regulations.

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

6.5.1 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

6.6 Treatment Compliance

Not applicable.

[redacted]

7 DISCONTINUATION CRITERIA

7.1 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 AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Termination of the study or the program by BMS.

- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.
- If study medication has been interrupted for low blood pressure, resumed, and an episode of hypotension (or symptoms of hypotension) reoccurs.
- Occurrence of pregnancy.

Refer to the Schedule of Activities (Section 1.3) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

In the case of pregnancy, the investigator must immediately notify the Medical Monitor/designee of this event. In the event a female participant becomes pregnant during a clinical trial, the study treatment must be discontinued immediately. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please notify the Medical Monitor within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator, the Medical Monitor/designee, and the patient must occur.

All participants who discontinue study treatment should comply with protocol-specified follow-up procedures as outlined in the Schedule of Activities, Section 1.3. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

7.1.1 Post-Study Treatment Study Follow-Up

In this study, follow-up is a key endpoint of the study. Post-study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 4 until death or the conclusion of the study.

Participants who discontinue study treatment may continue to be followed.

7.2 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 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.

7.3 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 **3** 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.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Medical Monitor 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 (Section 1.3), 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 (Section 1.3).

8.1 Efficacy Assessments

8.1.1 Urinary Output

4-Hour urinary output after the 40 mg furosemide bolus will be measured at the time points indicated in the Schedule of Activities (Section 1.3) and Table 8. The 4-hour urinary output after the 40 mg furosemide bolus in the BMS-986231 treatment period will be compared to baseline (4-hour urinary output after 40 mg furosemide bolus in placebo period).

8.1.2 Fractional Excretion of Na (FeNa) and K (FeK)

The plasma and urine concentrations of Na and K will be measured at the time points in the Schedule of Activities (Section 1.3), in Table 7 (blood sampling time points) and in Table 8 (urine collection intervals). The FeNa (%), FeK (%) and the concentration ratio of urinary sodium to urinary furosemide after the 40 mg furosemide bolus (collected 4-8 hours post-start infusion) will be compared to baseline (4-8 hour levels post-start infusion placebo period).

8.1.3 Imaging Assessment for the Study

Echocardiography

Assessments will be done at the time points indicated in the Schedule of Activities (Section 1.3).

Echocardiography to assess congestion: A targeted echo protocol will be implemented with assessment of the diameter of inferior vena cava (IVC), LV systolic and diastolic volumes, Ejection Fraction (Simpson), ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e'), left atrial (LA) volumes (min and max), visual assessment of mitral regurgitation (MR) and tricuspid regurgitation (TR), tricuspid annular plane systolic excursion (TAPSE)/pulmonary artery systolic pressure (PASP) and jugular venous diameter.

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

Lung Ultrasound

Lung ultrasonography (LUS) has emerged as a noninvasive, semi-quantitative diagnostic tool for the assessment of extravascular lung water in HF. B-lines on LUS are vertical, hyperechogenic artifacts which arise from the pleural line and can be quantified. B-lines count showed higher sensitivity than the clinical examination or chest radiography in the identification of pulmonary edema. B-lines counts (28 zones) will be done at the time points indicated in the Schedule of Activities (see Section 1.3) prior to start of study drug infusion, just before furosemide bolus and end of infusion.

Whole Body Bio-impedance

Noninvasive cardiac system (NiCaS) device will non-invasively assess CO, stroke volume index, total body water, total peripheral resistance based on whole body bio-impedance; it has been

demonstrated to meet Food and Drug Administration (FDA) standards for bioequivalence when compared to thermodilution-based CO methods.[31]

8.2 Adverse Events

The definitions of an AE or SAE can be found in APPENDIX 3.

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

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

Contacts for SAE reporting specified in APPENDIX 3.

8.2.1 Time Period and Frequency for Collecting AE and SAE Information

The Reference Safety Information in Sections 5.6.1 and 5.6.2 of the IB[16] should be used to determine the expectedness of SAEs for expedited reporting.

The collection of nonserious AE information should begin at initiation of study treatment until 24 hours after end of infusion in each treatment period of dosing (Schedule of Activities in Section 1.3). 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.

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 30 days of discontinuation of dosing.

- After these time periods, the investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure (eg, a follow-up skin biopsy).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the paper Safety Report Form.
- 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 PRA Drug Safety within 24 hours of updated information being available.

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

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

8.2.2 Method of Detecting AEs and SAEs

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

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

All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 7.3).

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

8.2.4 Regulatory Reporting Requirements for SAEs

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

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

8.2.5 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 PRA Drug Safety of this event and complete and forward a Pregnancy Surveillance Form to PRA Drug Safety within 24 hours of awareness of the event and in accordance with 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).

Any pregnancy that occurs in a female partner of a male study participant should be reported to PRA Drug Safety. In order for the 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.

8.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the AE CRF page. If a laboratory test result meets the definition of a serious adverse event, the laboratory test result should be reported as an SAE and submitted to PRA Drug Safety as specified in APPENDIX 3.

- Any laboratory test result that is clinically significant or meets the definition of an AE or 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).

8.2.7 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 8.2 and APPENDIX 3 for reporting details).

Potential DILI is defined as:

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

AND

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

AND

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

8.2.8 Other Safety Considerations

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

8.3 Overdose

All occurrences of overdose must be reported as SAEs (see Section 8.2).

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 8.2).

BMS-986231

Since there is limited clinical experience with BMS-986231, there is no current knowledge with overdosing, hence no specific guidance is currently available. In case of acute overdose, it is not known if dialysis would accelerate drug clearance. BMS-986231 produces vasodilation as a component of its hemodynamic effects. Thus, the most immediate adverse effect in the case of overdose of BMS-986231 may be hypotension, mediated at least in part by mechanisms similar to the hypotensive activity of IV nitroglycerin through activation of soluble guanylate. No specific pharmacologic antidote to HNO effects exists. In previous studies with BMS-986231 in healthy volunteers and advanced HF subjects, cessation of drug was adequate to restore blood pressure within 1-2 hours. In the event of an overdose, the infusion should be discontinued, and other therapies administered concurrently that have vasodilatory effects should be discontinued. Volume repletion, either orally or intravenously, can be used to counter the clinical effects of HNO mediated vasodilation, but should be used with extreme caution in decompensated HF subjects. If marked hypotension occurs, appropriate treatment, including IV pressor agents may be required to support blood pressure.

Furosemide

The principal signs and symptoms of overdose with furosemide are dehydration, blood volume reduction, hypotension, electrolyte imbalance, hypokalemia and hypochloremic alkalosis, and are extensions of its diuretic action. The acute toxicity of furosemide has been determined in mice, rats and dogs. In all 3, the oral LD50 exceeded 1000 mg/kg body weight, while the IV LD50 ranged from 300 to 680 mg/kg. The acute intragastric toxicity in neonatal rats is 7 to 10 times that of adult rats. The concentration of furosemide in biological fluids associated with toxicity or death is not known. Treatment of overdosage is supportive and consists of replacement of excessive fluid and electrolyte losses. Serum electrolytes, carbon dioxide level and blood pressure should be determined frequently. Adequate drainage must be assured in patients with urinary bladder outlet obstruction (such as prostatic hypertrophy). Hemodialysis does not accelerate furosemide elimination.

8.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 1.3).

8.4.1 Physical Examinations

Refer to Schedule of Activities (Section 1.3).

8.4.2 Vital Signs

Refer to Schedule of Activities (Section 1.3). Vital Signs (blood pressure and heart rate) will be recorded after the participant has rested quietly for at least 5 minutes in a supine position.

8.4.3 Peripheral Oxygen Saturation

Refer to Schedule of Activities (Section 1.3). Peripheral oxygen saturation will be recorded after the participant has rested quietly for at least 5 minutes in a supine position.

8.4.4 Electrocardiograms

Refer to Schedule of Activities (Section 1.3).

All ECG recordings must be performed using a standard high-quality, high-fidelity machine equipped with computer-based interval measurements and automated interpretation. Automated ECG intervals and HR will be captured or calculated, and changes of the T-wave and U wave morphology will be documented. ECG will be recorded after the participant has rested quietly for at least 5 minutes in a supine position.

8.4.5 Continuous Cardiac Monitoring (Telemetry)

Refer to Schedule of Activities (Section 1.3).

Continuous ECG monitoring will be performed to help monitor patient safety, primarily to detect ventricular and atrial arrhythmias. The site will follow their normal operating procedures established for ECG monitoring by trained staff. Clinically significant findings from the monitoring will be recorded as AEs and SAEs per investigator's decision, and at the investigator's discretion the infusion may be discontinued for clinically significant arrhythmias.

8.4.6 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report. Subjects will have laboratory tests performed as described in the following sections. A central/local laboratory will perform the analyses and will provide reference ranges for these tests.

Laboratory assessments for screening

The following laboratory tests will be performed as part of the screening evaluation. Results will be recorded in the study eCRF.

Hematology

- Hemoglobin
- Hematocrit
- White blood cell count and differential
- Platelet count

Serum Chemistry

- Aspartate Aminotransferase (AST, SGOT)
- Alanine Aminotransferase (ALT, SGPT)
- Blood Urea Nitrogen (BUN)
- Electrolytes
  - Sodium
  - Potassium
- Serum Creatinine (Scr)

- eGFR by equation used locally

Other Analyses

- BNP or NT-pro BNP (according to local lab availability) will be performed at screening.
- Pregnancy test (WOCBP only: screening, pre-dose (before start of infusion) in each treatment period).

On each treatment day, the study drug infusion could start without waiting for the results of the laboratory assessments done in the morning of the treatment day at the study facility if the following criteria are met:

- The results of the laboratory assessment at screening / previous period are within ranges compatible with inclusion criteria.
- The study participant was medically stable with no signs of overt HF decompensation or deteriorating signs and symptoms of congestion and without change in medication since the screening visit / previous period.

Laboratory Assessments During Study

The following laboratory tests will be performed and submitted to the Laboratory or Sponsor designated vendors for analysis as per the Study Assessment and Procedures.

Analyses		Timing
Hematology	• Hemoglobin • Hematocrit • White blood cell count, including differential • Platelet count	H0 (before start of infusion), H4 and H8 on each treatment day
Serum Chemistry	• Aspartate Aminotransferase (AST, SGOT) • Alanine Aminotransferase (ALT, SGPT) • Total bilirubin • Serum Creatinine (Scr) • eGFR • BUN	H0 (before start of infusion), H4 and H8 on each treatment day
	• Electrolytes: Na, K, Creatinine, eGFR • Bicarbonate, free water clearance	H0 (before start of infusion), H4, H5, H6, H7, H8 on each treatment day
Furosemide	• Furosemide plasma concentration	Please refer to Table 7
[redacted]	[redacted]	[redacted]
Urinalysis	• Fractional excretion of sodium • Fractional excretion of potassium • Urine Na, K, bicarbonate, creatinine, urea, phosphate, chloride, urine albumin-to-creatinine ratio (uACR) • Furosemide urinary concentration • Exploratory urinary biomarkers: including but not limited to urine kidney injury molecule-1 (KIM1)	Please refer to Table 8 [redacted]

The detailed methods for specimen collection, handling, processing, shipping, and storage will be supplied in the Investigator's Laboratory Manual provided by the Laboratory.

8.4.7 Suicidal Risk Monitoring

Not applicable.

8.4.8 Imaging Safety Assessment

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

8.5 Pharmacokinetics

Pharmacokinetic data of furosemide and BMS-986231 (and its metabolites) will be derived from plasma and urine concentration versus time data.

The primary possible PK parameters to be assessed for BMS-986231 (and its metabolites) and furosemide are included in Table 6:

Table 6: Potential Pharmacokinetic Parameters Calculated for Furosemide

Cmax	Maximum observed plasma concentration
AUC(INF)	Area under the concentration-time curve from time 0 extrapolated to infinity
AUC(0-T)	AUC from time 0 up to time T, where T is the last time point with concentrations above the lower limit of quantitation
Ae	Total amount recovered in urine
% UR	Percent urine recovery
CLR	Renal clearance of drug from plasma

Additional PK parameters may be calculated as deemed appropriate.

The plasma and urine samples for furosemide and BMS-986231 (and its metabolites BMT-284730 and BMT-279554) will be analyzed by a quantitative liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay.

Blood samples will be collected for PK assessments as described in Table 7. Urine samples can be taken from the urine collection intervals as described in Table 8. Detailed instructions for the PK blood and urine collection, labeling, processing, storage, and shipping will be provided to the site in the Laboratory Manual.
In addition, collect a PK sample from the patient when the dose is lowered due to a safety event and also at time of early discontinuation of study drug. The sample should be collected immediately before or after the decision to change the dose was made.

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

8.5.1 Blood Sampling and Urine Collection Intervals for PK and Efficacy

Blood sampling time points for furosemide, BMS-986231 (and its metabolites), Na and K are indicated in Table 7.

Table 7: Blood Sampling for Furosemide, BMS-986231 (and its metabolites)

Study Day of Sample Collection (of Each Period)	Event	Time (Relative To Start of Infusion of BMS-986231) Hour: Min	Blood Sample
1	Before start of infusion[a]	00:00	X
1	2.0 hours[a]	02:00	X
1	4.0 hours[b]	04:00	X
1	5.0 hours	05:00	X
1	6.0 hours	06:00	X
1	8.0 hours (EOI)[c]	08:00	X
1	10.0	10:00	X
1	Dose lowered due to safety event	Misc.	X

[a] This time-point is not applicable for furosemide analysis

[b] Just before furosemide bolus

[c] EOI=End of Infusion, This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. If end of infusion occurs prior to 8 hours after start of infusion (H8), the end of infusion should be considered early discontinuation. In case of an early discontinuation, the timing for the assessments will be adapted accordingly, ie, H8 will be immediately after end of infusion and H10 will be 2 hours after infusion.

Time points for urine collection intervals are presented in Table 8.

Table 8: Urine Collection Intervals for Urine Output and Assessment of Furosemide, BMS-986231, K, Na, P, Bicarbonate, Creatinine, and Cl

Study Day of Sample Collection (of Each Period)	Event	Time (Relative To Start of Infusion of BMS-986231) Hour: Min	Urine Sample Collection Intervals[a]
1	Before start of infusion	00:00	X
1	2.0 hours	02:00	0-2 hours
1	4.0 hours[b]	04:00	2-4 hours
1	5.0 hours	05:00	4-5 hours
1	6.0 hours	06:00	5-6 hours
1	7.0 hours	07:00	6-7 hours
1	8.0 hours (EOI)[c]	08:00	7-8 hours
1	10.0 hours	10:00	8-10 hours

[a] In the first 4 hours of the study drug infusion, and before furosemide bolus, urine collection will be done every 2 hours, thereafter the void will be hourly

[b] Just before furosemide bolus

[c] EOI=End of Infusion, This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. If end of infusion occurs prior to 8 hours after start of infusion (H8), the end of infusion should be considered early discontinuation. In case of an early discontinuation, the timing for the assessments will be adapted accordingly, ie, H8 will be immediately after end of infusion and H10 will be 2 hours after infusion.

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.6.1 Additional Research Collection

This protocol will include residual sample storage for additional research. All samples, including all residual samples may be stored and the exploratory research with these samples described in the protocol may continue for 15 years post end of study, which is defined as 2 years after the final study report. The scope of work involves using serum, plasma, to assess markers of heart failure, cardiac remodeling, neurohormonal activation, angiogenesis, oxidative and myocyte stress, renal function, congestion, inflammation, and fibrosis and associated diseases and pathways. Work may also include studies on the HNO pathway and mechanism of action as well as any pathways impacted by BMS-986231, as well as development of new or improved assays for pathway and functional markers associated with either BMS-986231and cardiovascular diseases. The goal is to better understand HF, cardiovascular and associated diseases/syndromes and any effects of the drug, BMS-986231.

Sites in the United States

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

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

For non-US Sites

Additional research is optional for all study participants, except where retention and/or collection of such samples is prohibited by local laws or regulations, ECs, or institutional requirements. Participants (or legally authorized representatives, as applicable) will be required to provide separate informed consent to participate.

Sample Collection and Storage

All serum, plasma, and urine samples from PK, pharmacodynamic and exploratory biomarker collections (as defined in Table 8, [redacted] may be retained for additional research purposes as described above. Samples kept for future research will be stored at the Sponsor biorepository or an independent, Sponsor-approved storage vendor.

- The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than 15 years after the end of the study or the maximum allowed by applicable law
- Transfers of samples by research Sponsor to third parties will be participant to the recipient's agreement to establish similar storage procedures

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

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

8.6.2 Immunogenicity Assessments

Not applicable.

8.7 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.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

The number of subjects to be enrolled was chosen based on practical considerations. Approximately 20 patients with HFrEF will be randomized in a 1:1 ratio to one of 2 sequences: BMS-986231/furosemide followed by placebo/furosemide or placebo/furosemide followed by BMS-986231/furosemide. The difference between BMS-986231 and placebo in total urine output in the 4 hours following furosemide administration will be estimated and presented with 95% confidence intervals (CIs).

Normal healthy volunteers have a urinary output around 0.5-1.0 mL/kg/H (40-100 mL/H), which could be decreased in people over 65 years old or patients with HF at around 0.2-0.5 mL/kg/H

(20-40 mL/H). Patients with HF given a bolus of IV loop diuretics is estimated to have their diuresis increased to 250-300 mL/H in the 4 hours following the administration. Assuming the standard deviation of urine output change is 20~35 mL/H based on the estimated range of the changes, with 20 patients, the study will be able to demonstrate a 20% increase in urinary output compared to placebo, with 90% power.

9.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent.
Randomized	All randomized subjects who have started study drug infusion in at least one treatment period. This is also known as the Intent to Treat (ITT) population. Data in this data set will be analyzed based on randomized sequence of treatments.
Treated (per protocol)	All randomized participants who were given both study treatments and completed the study as per protocol. Participants will be included in the treatment group they received in each period.
Safety	All randomized participants who take at least 1 dose of double-blind study treatment. Participants will be included in the treatment group they received in each period.

9.3 Endpoints

9.3.1 Primary Endpoint

- The total volume of urinary output 4 hours after 40 mg furosemide bolus given to patients with HFrEF while on BMS-986231 compared to placebo: absolute difference in total volume and % change from placebo.

9.3.2 Secondary Endpoints

- FeNa, FeK, furosemide urinary and plasma concentration and ratio urinary sodium to urinary furosemide at 8 hours post-start infusion. Parameter values while patient is on BMS-986231 compared to placebo: absolute differences and % change from placebo.

9.3.3 Safety Endpoints

- Clinically relevant hypotension (defined as SBP < 90 mmHg or symptomatic hypotension) during infusion, incidence of AEs, abnormal clinical laboratory values, vital signs, ECGs, telemetry, physical examinations.

[redacted]

9.4 Statistical Analyses

The statistical analysis plan (SAP) 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. For analyses involving baseline, the baseline value is defined as the last value prior to the start of infusion for the specific period, unless otherwise noted.

9.4.1 Efficacy Analyses

9.4.1.1 Primary Efficacy Analysis

All primary efficacy analyses will be performed using the treated (per protocol) population. Total amount of urine excreted over 4 hours after a bolus injection of 40 mg furosemide while receiving BMS-986231 or placebo will be summarized and analyzed. Volumes at each urinary collection

interval as well as total volume will be tabulated. Graphical presentations may be provided. All data will be listed.

A within patient analysis using a paired T-test will be performed to compare the volumes of urinary excretion and to test if there is a significantly different amount of urine secreted while receiving BMS-986231 versus placebo.

9.4.1.2 Secondary Efficacy Analysis

Secondary efficacy analyses will be performed using the randomized population. The FeNa, FeK, furosemide urinary and plasma concentration and the ratio of urinary sodium to urinary furosemide will be calculated at each time point over 4-hour urine/plasma collection after a bolus injection of 40 mg furosemide while receiving BMS-986231 or placebo. All data will be listed and tabulated. Graphical presentations may be provided.

A similar analysis as described in the primary efficacy analysis section will be conducted on the values derived at the 8-hour time point (8 hours after start of infusion).

9.4.2 Safety Analyses

All safety analyses will be performed on the safety population (see Section 9.2). For safety analyses, all recorded AEs for each period will be listed and tabulated by system organ class, preferred term and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings, and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed.

9.4.3 Pharmacokinetic Analyses

Descriptive summaries will be presented for continuous variables using number of participants (n), mean, standard deviation (SD), median, minimum, and maximum. Descriptive summaries of PK data will additionally include geometric mean and coefficient of variation (CV%). Descriptive summaries for categorical variables will utilize counts (n) and percentages (%).

9.4.4 Other Analyses

Results for other endpoints will be summarized descriptively. Model-based analyses may be performed, using models similar to the model for the primary endpoint.

9.4.5 Interim Analyses

Not applicable.

11 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ACC	American College of Cardiology
ACEi	angiotensin-converting-enzyme inhibitor
ADHF	acute decompensated heart failure
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AHA	American Heart Association
AHF	acute heart failure
ALT	alanine aminotransferase
ARB	angiotensin-receptor blockers
ARNI	angiotensin-receptor/neprilysin inhibitor
AST	aspartate aminotransferase
AVP	arginine-vasopressin system
BMS	Bristol-Myers Squibb
BNP	brain natriuretic peptide
bpm	beats per minute
BUN	blood urea nitrogen
CA125	cancer antigen 125
CI	cardiac index
CIs	confidence intervals
CONSORT	Consilidated Standards of Reporting Trials
CRF	case report form
CV	cardiovascular
CVA	cerebrovascular accident
D5W	5% dextrose in water
DBP	diastolic blood pressure
DILI	drug induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DTI	doppler tissue imaging
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ESC	European Society of Cardiology
FDA	Food and Drug Administration
HCG	human chorionic gonadotropin
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HNO	Nitroxyl

Term	Definition
HR	heart rate
IB	investigator brochure
IEC	independent ethics committee
I(M)P	investigational (medicinal) product
IRB	institutional review board
ITT	intent to treat
IV	intravenous
K+	Potassium
LA	left atrium
LC-MS	liquid chromatography–mass spectrometry
LDH	lactate dehydrogenase
LV	left ventricle
LVEF	left ventricular ejection fraction
mARC	mitochondrial amidoxime-reducing component
MI	myocardial infarction
MMRM	mixed model repeated measures
MRA	mineralocorticoid receptor antagonists
MRI	magnetic resonance imaging
MUGA	multigated acquisition
MVO2	myocardial oxygen consumption
Na+	Sodium
NCV	nerve conduction velocities
N-GAL	gelatinase-associated lipocalin
NiCaS	noninvasive cardiac system
NO	nitric oxide
NT-pro BNP	N terminal- pro BNP
NYHA	New York Heart Association
PASP	pulmonary artery systolic pressure
PCWP	pulmonary capillary wedge pressure
PDE5	phosphodiesterase type 5
pH	potential of hydrogen
PK	pharmacokinetic
RA	right atrium
RAAS	renin-angiotensin-aldosterone system
RAP	right atrial pressure
RV	right ventricle
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
sCD146	cluster of differentiation 146

Term	Definition
Scr	serum creatinine
SD	standard deviation
SERCA	sarcoplasmic reticulum calcium adenosine triphosphatase
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SNS	sympathetic nervous system
SUSAR	suspected, unexpected serious adverse reaction
TAPSE	tricuspid annular plane systolic excursion
TIA	transient ischemic attack
TR	tricuspid regurgitation
uACR	urine albumin-to-creatinine ratio
ULN	upper limit of normal
WOCBP	women of child bearing potential

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), AE tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of

original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY TREATMENT RECORDS

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

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

	These records should include: • label identification number or batch number • amount dispensed to and returned by each 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 collected and reported on the paper Safety Report Form and paper Pregnancy Surveillance Form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF, Safety Report Form, or Pregnancy Surveillance Form completion guidelines provided by PRA.

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 and/or pregnancy forms, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections. Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

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.

For this study, study treatments (those supplied by BMS or its vendors) such as full or partially used study treatment containers, vials, syringes cannot be destroyed on site.

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

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

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

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (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 treatment and that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

Events Meeting the AE Definition

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

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

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

Serious Adverse Event Definition: 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 or permanent damage
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 8.2.7 for the definition of potential DILI.)

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see section 8.2.5 for reporting pregnancies).

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

EVALUATING AES AND SAES

Assessment of Intensity

The intensity of AEs is determined by a physician and will use the following levels:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

Assessment of Causality

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

Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. Note: Follow-up SAE reports must include the same investigator term(s) initially reported. If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

SAEs, whether related or not related to study drug, and pregnancies must be reported to PRA Drug Safety within 24 hours of awareness of the event.

SAEs must be recorded on the SAE Report Form. 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.

Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission to:

[redacted]

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 postmenopausal 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 judgment 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

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as # Days/ Weeks Relevant Exposure days/weeks after the end of study treatment, plus 30 days.

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

Highly Effective Methods That Are User Independent
• Nonhormonal intraurine devices (IUDs), such as ParaGard ® • 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.*
• Complete 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.* • Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the investigational drug plus 30 days) • 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

Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus) • Spermicide only • Lactation amenorrhea method (LAM)

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
- Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and IUDs such as Mirena ®
- Intrauterine hormone-releasing system (IUS)
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Male or female condom with or without spermicide*. Male and female condoms cannot be used simultaneously

[redacted]

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 91 Days after discontinuation (duration of study drug plus 90 days [duration of sperm turnover] of treatment in the male participant.
- Female partners of males participating in the study to consider use of effective methods of contraception until 91 Days after discontinuation (duration of study drug plus 90 days [duration of sperm turnover] 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 91 Days after discontinuation (duration of study drug plus 90 days [duration of sperm turnover] of treatment in the male participant.
- Refrain from donating sperm for the duration of the study treatment until 91 Days after discontinuation (duration of study drug plus 90 days [duration of sperm turnover] of treatment in the male participant .

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 8.2.5 and the APPENDIX 3 for AE and SAE Definitions and procedures for Evaluating, Follow-up and Reporting.