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CLINICAL PROTOCOL CV013020

A Multicenter, Randomized, Double-Blind, Placebo- and Active-Controlled, Cross-over Phase 2 Study of Continuous 5-Hour Intravenous Infusions of BMS-986231 in Patients with Heart Failure and Impaired Systolic Function

Revised Protocol: 05

Study Director

Medical Monitor
Maria Borentain MD

to partners to which BMS has transferred obligations, e.g., a Contract Research Organization (CRO).

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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 05	24-Jan-2019	Clarified the wording the Appendix 3 to harmonize AE definitions in BMS clinical studies. Clarified the enrollment numbers under study drug.
Revised Protocol 04	05-Sep-2018	Incorporating Administrative Letters 03 and 04 content that was not included in Revised Protocol 03
Revised Protocol 03	17-Jul-2018	[redacted]
Administrative Letter 04	02-Feb-2018	To clarify the origin of Nitroglycerin supplied by BMS.
Administrative Letter 03	26-Oct-2017	Correct minor typographical errors identified throughout the protocol.
Revised Protocol 02	01-Sep-2017	Clarification of allowable contraceptives for WOCBP, addition of chronic nitrates use criteria, clarification of IP preparation, handling and storage
Administrative Letter 02	12-Jul-2017	Clarification of IP formulation as vials or ampules.
Administrative Letter 01	05-Jul-2017	Clarification of follow-up phone call 30 days after the end of the infusion of the last period (will assess occurrence of any SAEs)
Revised Protocol 01	14-Jun-2017	Inserted additional text into Section 8.1: 'Discontinuation from Study Treatment' to allow the patient to be part of the IP continuation discussion when confirmed pregnant.
Original Protocol	22-May-2017	Not Applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 05:

The rational for updating this protocol is that the current version of Appendix 3 directs that disease-related events do not meet the AE definition and, therefore, should not be reported as AEs. The update is part of a larger effort to harmonize AE definitions in BMS clinical studies and more particularly to allow reporting of any type of disease-related events.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 3	Updated Appendix 3 to clarify the collection of disease related events.	The current version directs that disease-related events do not meet the AE definition and, therefore, should not be reported as AEs. Unnecessary text was deleted to clarify that disease related events and events associated with lack of efficacy will need to continue to be reported as AEs if the event meets the criteria of an AE while text was added to clarify the need to report abnormal lab tests or other safety assessments when the final diagnosis is not available. Content was added to clarify the need for the investigator to report the specific term of "intentional overdose" as an AE term. The change is part of a larger effort to harmonize AE definitions in BMS clinical studies and more particularly to allow reporting of any type of disease-related events.
Summary	Clarified the enrollment numbers were approximately 42 participants	Brought the enrollment number estimates to align with other sections of the protocol.
Section 5.1	Clarified the enrollment numbers were approximately 42 participants	Brought the enrollment number estimates to align with other sections of the protocol.
Section 9.4.4	Corrected to inclusion/exclusion criteria	Corrected a typographical error from the incorporation of Administrative Letter 03 during Revised Protocol 04

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Objectives and Endpoints:

Table 1-1: Objectives and Endpoints

Objectives	Endpoints
Primary • Evaluate the effects of BMS-986231 on the left ventricular (LV) systolic function by stroke volume index (SVI) assessed by echocardiography compared to placebo.	• Mean SVI derived from the velocity time integral at the left ventricular outflow tract (LVOT VTI) at the end of the 5-hours infusion of BMS-986231, versus placebo.
Secondary • Evaluate the effects of BMS-986231 on the left ventricular (LV) systolic function by stroke volume index (SVI) assessed by echocardiography compared to nitroglycerin (NTG). • Evaluate the effects of BMS-986231 on selected other left ventricular systolic and diastolic indices compared to placebo and NTG	• Mean SVI derived from LVOT VTI at the end of the 5-hours infusion of BMS-986231, versus NTG. • Mean LVEF, computed by Simpson's method at the end of the 5-hours infusion of BMS-986231, versus placebo and NTG. • Mean cardiac power index at the end of the 5-hours infusion of BMS-986231, versus placebo and NTG. • Mean Diastolic indices: E/A, annular e' velocity and E/e' ratio at the end of the 5-hours infusion of BMS-986231, versus placebo and NTG. • Mean LV global longitudinal strain, computed using STE at the end of the 5-hours infusion of BMS-986231, versus placebo and NTG.

Overall Design:

This is a multi-center, randomized, cross-over, placebo and active-controlled, double-blind, study of continuous 5-hour intravenous (IV) infusion of BMS-986231 in patients with heart failure and reduced ejection fraction (HFrEF). The trial is designed to evaluate the effects of BMS-986231on systolic and diastolic parameters measured by echocardiography.

Design

A cross-over design will be implemented in this trial, every subject will be exposed to each of the 3 interventions in 3 treatment periods (BMS-986231, NTG and placebo) with one intervention occurring during each treatment period, including the 5-hour infusion, followed by a washout period of at least 5 days, but no more than 4 weeks.

Study drug

Approximately 42 study participants will be randomized to receive BMS-986231, NTG, and placebo, in one of the 6 possible sequences.

NTG, BMS-986231 and placebo: will be administered as a 5-hours infusion according to an up-titration schedule, which is achieved by an increase in the infusion flow rate. All three interventions

(NTG, BMS-986231 and placebo) will have the same flow rate as follows: 5 mL/H for 10 min, followed by 10 mL/H for 10 minutes then 20 mL/H for the rest of the infusion.

The corresponding doses of the active study medications will be:

- NTG: 20 µg/min for 10 min, followed by 40 µg/min for 10 min, followed by 80 µg/min for the rest of the 5-hour infusion;
- BMS-986231: 3 µg/kg/min for 10 min, followed by 6 µg/kg/min for 10 min, followed by 12 µg/kg/min for the rest of the 5-hour infusion.

In case of decrease in systolic blood pressure, an algorithm will be used to down-titrate / interrupt or discontinue the study drug infusion (see section 7.4 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 including assessment of ejection fraction, suitability of echocardiography windows and image quality. 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 6 sequences that will be conducted in parallel.

If the period 1 treatment day could only be scheduled beyond 4 weeks from screening, a consultation with the medical monitor is needed to identify which screening procedure should be repeated prior to randomization.

Treatment day (Day 1 of each period)

Study participants will be admitted to the study facility on the treatment day, which will be the Day 1 of each of the three periods. Assessment of vital signs and laboratory tests will be performed pre-dose. In each treatment day, blood pressure and heart rate should be within the inclusion / exclusion criteria limits, and no atrial fibrillation or atrial flutter should be present in order to start the study treatment. 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/exclusion criteria,
- The study participant was medically stable without change in medication since the screening visit / previous period.

If the laboratory tests (e.g. electrolytes, serum creatinine, eGFR, hemoglobin, transaminases) prior to infusion, are not within inclusion and exclusion criteria limits, the study drug will be discontinued after consultation with the medical monitor. The abnormalities should be corrected before the next treatment period.

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), echocardiography, whole body bioimpedance and pulse wave analysis (non-invasive central aortic blood pressure) will be performed at selected times throughout the dosing interval. Participants

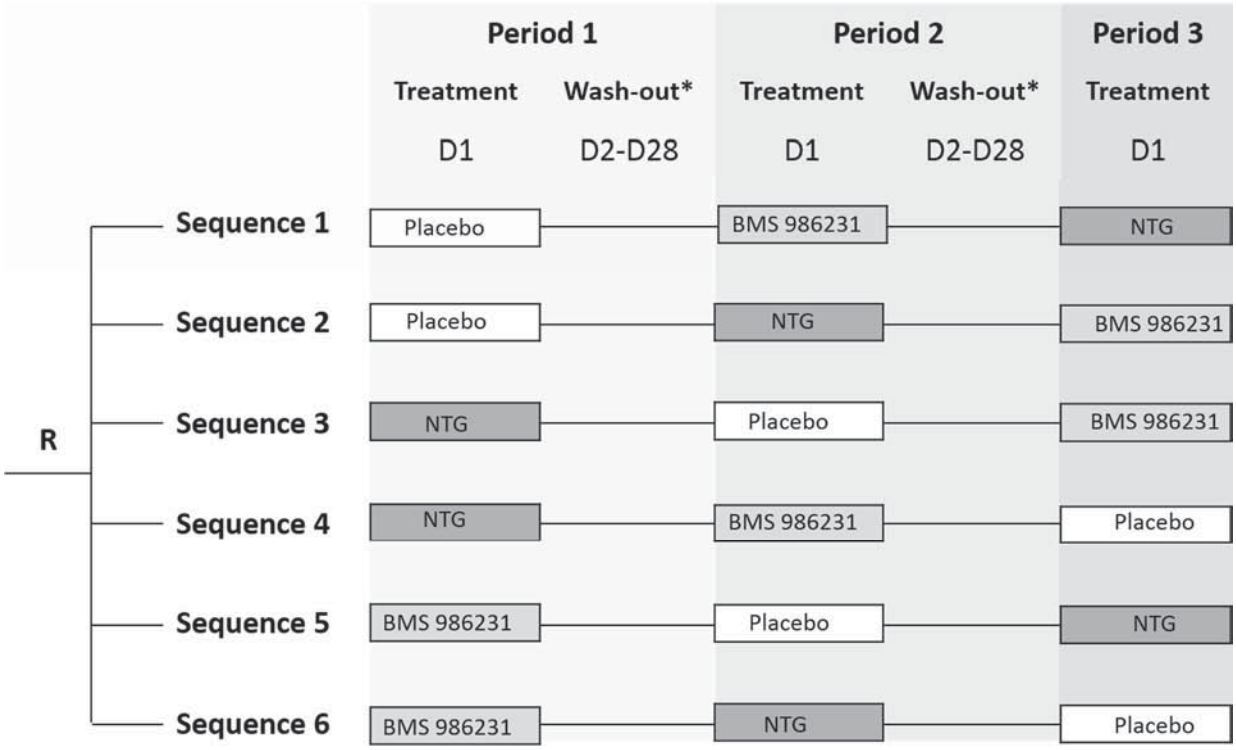
will be closely monitored for adverse events throughout the study. Blood samples will also be collected at selected intervals after the start of study drug administration for pharmacokinetic (PK) analysis.

Discharge

Study participants will remain in the study facility for approximately 3.5 hours post-dose and discharged on the same day, unless the investigator and the study team consider that an overnight stay is warranted. Same-day discharge is allowed if the following conditions are met:

- in the opinion of the investigator an overnight stay is not warranted,
- there is no hypotension after mobilization and
- 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.

Figure 1: Study design



***Wash-out period will be at least 5 days, but no more than 4 weeks**.

Number of Participants:

Sample sizes are calculated based on comparison of post-baseline values, adjusting for the differences in the baseline value. Sample size calculations assume an increase of the stroke volume index (SVI) of 4.5 mL/m² from baseline, relative to placebo, an inter-individual SD of 10 mL/m²,

and intra-individual correlations for the difference between assessments of 0.7. Approximately 36 subjects with data from treatment periods being compared will be required to achieve a power of 90%, with a type I error probability of 0.05 (2-sided). In order to address the potential for missing data arising from withdrawal from the study, an allowance of approximately 15% subjects will be included, with a resulting target sample size of 42 subjects to be randomized. An estimated 42 subjects will be randomized, in order to complete 36 subjects.

Randomized: 42

Key Inclusion / Exclusion Criteria:

Inclusion:

- Signed Written Informed Consent
- Age 18 years (or age of majority) or older
- Heart failure with reduced ejection fraction (LVEF on echocardiogram of 40% or less), as assessed by the echocardiographic core lab.
- Stable guideline directed therapy for heart failure (could include oral diuretics, ACEi, ARBs, ARNi, MRAs , and β blockers as tolerated), with no dose changes of these medications in the past 2 weeks
- Have screening values of NT pro-BNP ≥ 125 pg/mL (15 pmol/L) or BNP ≥ 35 pg/mL (10 pmol/L).
- In sinus rhythm at the start of the infusion

Exclusion:

- Body weight < 45 kg or ≥ 140 kg
- Low quality echocardiographic visualization windows and image acquisition
- Systolic blood pressure (SBP) < 110 mm Hg at screening or pre-randomization
- Heart rate < 50 beats per minute (bpm) or > 90 bpm at screening or pre-randomization
- Permanent Atrial Fibrillation, Atrial Flutter or having Atrial Fibrillation, Atrial Flutter before start of the infusion
- Permanent paced rhythm (VVI, DDD or BiV pacing)
- Ventricular assist device or prior heart transplant
- Primary HF etiology attributable to either restrictive/obstructive cardiomyopathy, idiopathic hypertrophic or uncorrected severe valvular disease as defined by AHA/ACC/ESC criteria.
- (Note: A restrictive mitral inflow pattern is NOT exclusionary)
- Large post-MI Left Ventricular aneurisms
- Intra-cardiac thrombus
- Prior mitral valve repair, mitral or aortic prosthesis

- Treatment with oral phosphodiesterase type 5 (PDE5) inhibitor sildenafil, vardenafil or avanafil within 24 hours of study drug infusion or treated with tadalafil within 4 days of study drug infusion
- Hospitalized for acute decompensated heart failure in the previous month
- Hospitalized with acute coronary syndrome, coronary revascularization or acute myocardial infarction during the previous 90 days prior to screening
- Have a history of a cerebral vascular accident (CVA or stroke) or of a transient ischemic attack (TIA) during the previous 90 days prior to screening
- NYHA Class IV symptoms of heart failure
- Treatment with intravenous inotropic therapy (dobutamine, milrinone, levosimendan) in the previous month or planned treatment in the next 3 months.
- Current treatment with chronic oral, transdermal or sublingual nitrates, except at the discretion of the investigator and treating physician, nitrates could be temporarily interrupted. In which case, an interruption of 3 days is required prior to start of study drug.
- Prior solid organ transplant
- Estimated glomerular filtration rate (eGFR) < 15 ml/min/1.73 m^2
- Have persistent abnormal serum electrolytes not resolved between screening and start of the study drug infusion, as defined by any of the following:
  - A sodium (Na+) concentration < 130 or >145 mEq/L (mmol/L)
  - A potassium (K+) concentration < 3.2 or >5.5 mEq/L (mmol/L)
- Have severe anemia, as documented by a hemoglobin < 9 g/dL (< 5.59 mmol/L)
- Liver disease defined as history of cirrhosis with evidence of portal hypertension such as varices, or encephalopathy, or total bilirubin > 3 mg/dL (> 51 μmol/L) or significant elevation of liver enzymes (AST, ALT > 3 times the upper limit of normal)
- Considered clinically unstable for any condition
- Serious comorbid non cardiovascular disease in which the life expectancy of the subject is < 3 months
- Known hypersensitivity or contra-indication to the intravenous echocardiography contrast agent, in case contrast echocardiography is used

2 SCHEDULE OF ACTIVITIES

Table 2.-1: Time & Event Schedule CV013020, Screening Period

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	
Concomitant medications	x	
Echocardiography eligibility assessment	x	As described in the echocardiographic core lab manual, evaluation of image quality and assessment of ejection fraction
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 and weight.
Vital Signs	x	Includes body temperature, respiratory rate, and seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
Adverse Events Assessment	x	SAEs must be collected from the date of the participant's Informed consent.
Local Laboratory Tests	x	Hematology, Serum chemistry, NT-proBNP or BNP (details in the protocol section 9.4.4)
Pregnancy Test (WOCBP only)	x	

Table 2.-2: Time & Event Schedule CV013020, Treatment and Follow-up Study Periods

Procedure	Treatment Period					Notes
	Period 1 Day 1	Washout 5-28 Days	Period 2 Day 1	Washout 5-28 Days	Period 3 Day 1	Washout between periods should be at least 5 days and no more than 4 weeks.
Safety Assessments						
Weight	x		x		x	Weight pre-and end of the infusion in each treatment period.
Targeted physical examination	x		x		x	Based on subject's report since the screening visit. Includes temperature, signs and symptoms of congestion.
Vital Signs (Blood pressure and heart rate)	x		x		x	Prior to infusion. 30 minutes at first hour, then every 1 hour until discontinuation of infusion, then at 1 hour, 2 hour and 3.5 hour after end of infusion in each treatment period .
Peripheral Oxygen Saturation	x		x		x	Prior and end of the infusion in each treatment period, measured with a pulse oximeter device.
12 lead ECG	x		x		x	Prior to the infusion and after end of infusion in each treatment period.
Urinary output	x		x		x	From start of infusion to 3 hours after end of infusion in each treatment period.
Telemetry	x		x		x	From start of infusion to 3 hours after end of infusion in each treatment period.
Adverse Events Assessment	x		x		x	Non-serious AEs will be collected from the start of the study drug infusion. until 24 hours after end of infusion in each treatment period of dosing in each period Serious adverse events must be collected from the date of Informed consent and will be assessed up to 30 days after the end of infusion of the last period.

Table 2.-2: Time & Event Schedule CV013020, Treatment and Follow-up Study Periods

Procedure	Treatment Period					Notes
	Period 1 Day 1	Washout 5-28 Days	Period 2 Day 1	Washout 5-28 Days	Period 3 Day 1	Washout between periods should be at least 5 days and no more than 4 weeks.
Concomitant Medications	x		x		x	Chronic heart failure medications to be taken during the treatment day (D1 of each period) will be withheld until the end of the study drug infusion in each treatment period.
Follow-up call	x		x		x	Follow-up call to be done at Day 2 of each period (will inquire about general status and occurrence of any AEs) and 30 days after the end of the infusion of the last period (will assess occurrence of any SAEs).
Local Laboratory Tests	x		x		x	Hematology and Serum chemistry (details in the protocol section 9.4.4). Can be performed within 24 hours of treatment day.
Central Laboratory Tests	x		x		x	Hematology, Serum chemistry, Urinalysis, Biomarkers (details in the protocol section 9.4.4)
Pharmacokinetic (PK) sampling	x		x		x	PK sampling will be done pre-dose, 0.5 hour, 1 hour, 4.5 hours and 7 hours after the start of the infusion in each treatment period. In addition, PK samples should be taken when the dose is lowered or in case of early discontinuation (see protocol section 9.5)
Pregnancy Test (WOCBP only)	x		x		x	Can be performed within 24 hours of treatment day.
Efficacy Assessments						
Echocardiography	x		x		x	Prior to and before the end of the study infusion (between hour 4 and hour 5) in each treatment period. If study drug is interrupted prematurely, the echocardiography assessment should be done as soon

Table 2.-2: Time & Event Schedule CV013020, Treatment and Follow-up Study Periods

Procedure	Treatment Period					Notes
	Period 1 Day 1	**Washout 5-28 Days**	**Period 2 Day 1**	**Washout 5-28 Days**	**Period 3 Day 1**	**Washout between periods should be at least 5 days and no more than 4 weeks.**
						as possible after study drug interruption. If the study drug is resumed after interruption, echocardiography should be repeated between hour 4 and hour 5 of the effective study drug infusion.
Whole body bioimpedance	x		x		x	Prior to infusion, at 1 hour and 3 hours after start of infusion, at end of infusion and 2 hours after the end of the infusion in each treatment period. In addition, should be performed after each supplementary echocardiographic assessment.
Pulse wave analysis	x		x		x	Prior to and at end of infusion in each treatment period, just after the echocardiographic assessment has been performed. In addition, should be performed after each supplementary echocardiographic assessment.
Administer Study Medication	x		x		x	5-hour continuous infusion ***Study medication to begin promptly after pre-infusion testing completed***
Clinical Drug Supplies						
Randomize	x					
Dispense Study Drug	x		x		x	
Additional Research Sampling						
Additional Research plasma	x		x		x	Sampling will be done pre-dose and 4.5 hours after the start of the infusion in each treatment period.
Blood sampling for DNA variants in mARC and ADME related genes	x					Sample can be collected at Period 1 Day1 or any other day, only one sample collection for each subject during the study.

In the event of multiple procedures are required at a single time point, the following order for performing the procedures is recommended:

- Safety
- Pharmacokinetic sampling
- Additional research sampling

3 INTRODUCTION

Heart failure 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[1,2]. Although advances in drug and device treatment of chronic heart failure over the past 40 years have led to improvements in outcome of these patients, the morbidity and mortality of heart failure remains high. In contrast, there have been few advances in the approach to treat episodes of acute decompensated heart failure (ADHF) over the same time period, and no therapies have been demonstrated to improve long-term clinical outcomes[3].

Standard of care therapies for ADHF are based on the use of intravenous diuretics to promote fluid removal to reduce dyspnea, and in some patients, oral or intravenous vasodilators, to reduce the load on the heart and improve cardiac performance[4]. Collectively, these treatments may reduce dyspnea but do not target the primary cause of heart failure, 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[5,6,7].

An agent that increases contractility, while avoiding the adverse safety profile of an inotropic agent and retaining the capacity to unloading 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, it's 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.

A study to characterize the cardiac effects of BMS-986231 on systolic and diastolic function will enhance the understanding of the mechanism of action of HNO, and better delineate the relative contributions of vasodilation, enhanced contractility, and improved relaxation on the effects of BMS-986231 on cardiac function. Such a mechanistic study may help inform future development by demonstrating a differentiated effect compared to nitro-vasodilators which do not enhance either cardiac contractility and or relaxation.

[redacted]

4 OBJECTIVES AND ENDPOINTS

Table 4.-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
Evaluate the effects of BMS-986231 on the left ventricular (LV) systolic function by stroke volume index (SVI) assessed by echocardiography compared to placebo.	Mean SVI derived from the velocity time integral at the left ventricular outflow tract (LVOT VTI) at the end of the 5-hours infusion of BMS-986231, versus placebo.
Secondary	
Evaluate the effects of BMS-986231 on the left ventricular (LV) systolic function by stroke volume index (SVI) assessed by echocardiography compared to nitroglycerin (NTG).	Mean SVI derived from LVOT VTI at the end of the 5-hours infusion of BMS-986231, versus NTG.
Evaluate the effects of BMS-986231 on selected other left ventricular systolic and diastolic indices compared to placebo and NTG: LV ejection fraction Mean LV power index Diastolic function LV global longitudinal strain	Mean LVEF, computed by Simpson's method at the end of the 5-hours infusion of BMS-986231, versus placebo and NTG. Mean cardiac power index at the end of the 5-hours infusion of BMS-986231, versus placebo and NTG. Mean Diastolic indices: E/A, annular e' velocity, and E/e' ratio at the end of the 5-hours infusion of BMS-986231, versus placebo and NTG. Mean LV global longitudinal strain, computed using STE at the end of the 5-hours infusion of BMS-986231, versus placebo and NTG.

[redacted]

Table 4.-1: Objectives and Endpoints

[redacted]

5 STUDY DESIGN

5.1 Overall Design

This is a multi-center, randomized, cross-over, placebo and active-controlled, double-blind, study of continuous 5-hour intravenous (IV) infusions of BMS-986231 in patients with heart failure and reduced ejection fraction (HFrEF). The trial is designed to evaluate the effects of BMS-986231on systolic and diastolic parameters measured by echocardiography.

Design

A cross-over design will be implemented in this trial, every subject will be exposed to each of the 3 interventions in 3 treatment periods (BMS-986231, NTG and placebo) with one intervention occurring during each treatment period, including the 5-hour infusion, followed by a washout period of at least 5 days, but no more than 4 weeks.

Study drug

Approximately 42 study participants will be randomized to receive BMS-986231, NTG, and placebo, in one of the 6 possible sequences.

NTG, BMS-986231 and placebo will be administered as a 5-hours infusion, according to an up-titration schedule, which is achieved by an increase in the infusion flow rate. All three interventions (NTG, BMS-986231 and placebo) will have the same flow rate as follows: 5 mL/H for 10 min, followed by 10 mL/H for 10 minutes then 20 mL/H for the rest of the infusion.

The corresponding doses of the active study medications will be:

- NTG: 20 μg/min for 10 min, followed by 40 μg/min for 10 min, followed by 80 μg/min for the rest of the 5-hour infusion;
- BMS-986231: 3 μg/kg/min for 10 min, followed by 6 μg/kg/min for 10 min, followed by 12 μg/kg/min for the rest of the 5-hour infusion.

In case of a decrease in systolic blood pressure, an algorithm will be used to down-titrate / interrupt or discontinue the study drug infusion (see section 7.4 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 including assessment of ejection fraction, suitability of echocardiography windows and image quality. 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 6 sequences that will be conducted in parallel.

If the first period of treatment day could only be scheduled beyond 4 weeks from screening, a consultation with the BMS/PPD medical monitor is needed to identify which screening procedure should be repeated prior to randomization.

Treatment day (Day 1 of each period)

Study participants will be admitted to the study facility on the treatment day, which will be the Day 1 of each of the three periods. Assessment of vital signs and laboratory tests will be performed pre-dose. In each treatment day, blood pressure and heart rate should be within the inclusion / exclusion criteria limits, and no atrial fibrillation or atrial flutter should be present in order to start the study treatment. 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/exclusion criteria,
- The study participant was medically stable without change in medication since the screening visit / previous period.

If the laboratory tests (e.g. electrolytes, serum creatinine, eGFR, hemoglobin, transaminases) prior to the infusion, are not within inclusion and exclusion criteria limits, the study drug will be discontinued after consultation with the medical monitor. The abnormalities should be corrected before the next treatment period.

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), echocardiography, whole body bioimpedance and pulse wave analysis (non-invasive central aortic blood pressure) will be performed at selected times throughout the dosing interval. Participants will be closely monitored for adverse events throughout the study. Blood samples will also be collected at selected intervals after start of study drug administration for pharmacokinetic (PK) analysis.

Discharge

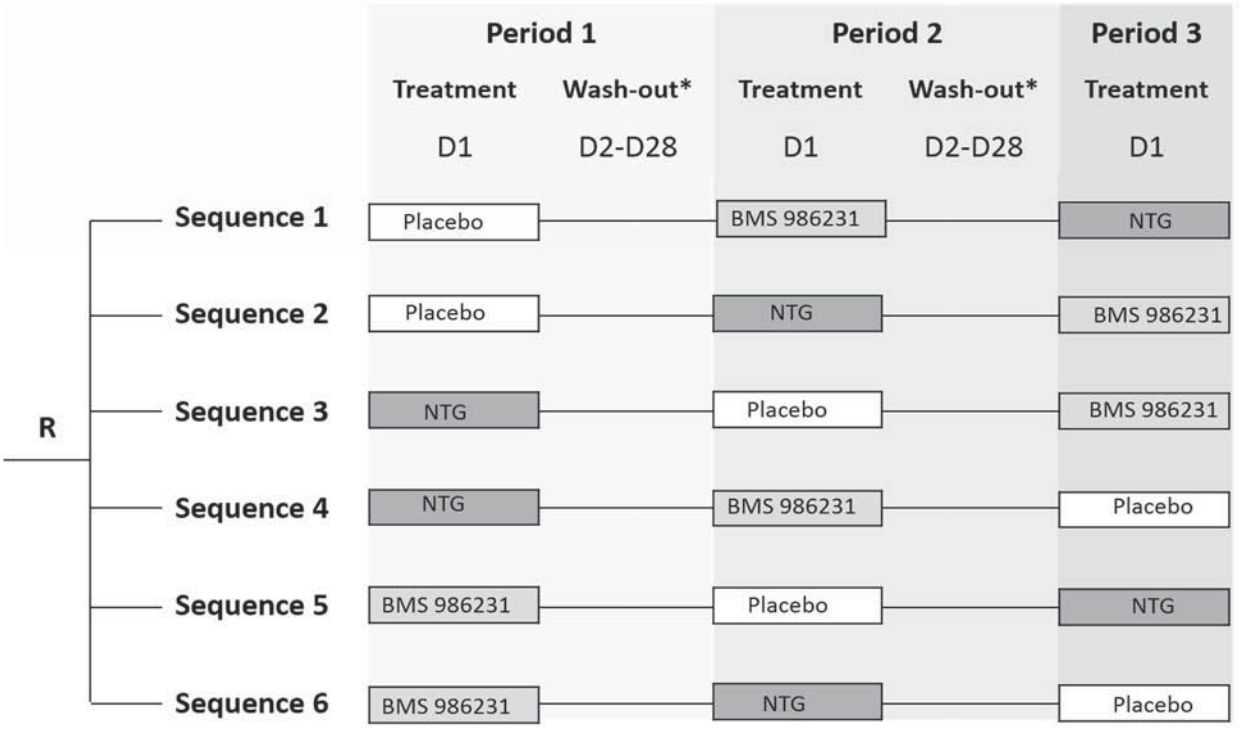
Study participants will remain in the study facility for approximately 3.5 hours post-dose and discharged on the same day, unless the investigator and the study team consider that an overnight stay is warranted. Same-day discharge is allowed if the following conditions are met:

- in the opinion of the investigator an overnight stay is not warranted,
- there is no hypotension after mobilization and

- 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 5.1-1

Figure 5.1-1: Study Design Schematic



* Was-out period will be at least 5 days, but no more than 4 weeks.

5.1.1 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 heart failure patients (NCT03016325)[25].

The executive committee will be a small body comprised of academic leaders. The executive committee will provide advice on overall design, study endpoints and recommendations for study sites, and will review results from final analyses with Sponsor.

5.2 Number of Participants

Sample size calculations assume an increase of the stroke volume index (SVI) of 4.5 mL/m² from baseline, relative to placebo, an inter-individual SD of 10 mL/m², and intra-individual correlations for the difference between assessments of 0.7. Approximately 36 subjects with data from treatment periods being compared will be required to achieve a power of 90%, with a type I

error probability of 0.05 (2-sided). In order to address the potential for missing data arising from withdrawal from the study and/or losses to follow-up, an allowance of approximately 15% subjects will be included, with a resulting target sample size of 42 subjects to be randomized. An estimated 42 subjects will be randomized, in order to complete the study with 36 subjects. Further details are provided in Section 10.

5.3 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 2, 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.

[redacted]

[redacted]

6 STUDY POPULATION

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

6.1 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) Heart failure with reduced ejection fraction (LVEF on echocardiogram of 40% or less)

c) Stable guideline directed therapy for heart failure including oral diuretics, ACEi, ARBs, ARNi, MRAs , and β blockers as tolerated), with no dose changes of these medications in the past 2 weeks

d) Have screening values of NT pro-BNP ≥ 125 pg/mL (15 pmol/L) or BNP ≥ 35 pg/mL (10 pmol/L).

e) In sinus rhythm at the start of the infusion

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 HCG) within 24 hours prior to the start of study treatment.

b) Women must not be breastfeeding

c) Women of childbearing potential (WOCBP) must agree to follow instructions for methods of contraception for 32 days after discontinuation (duration of study drug plus 30 days duration of one ovulatory cycle).

d) Males who are sexually active with WOCBP must agree to follow instructions for methods of contraception (Appendix 4) for total of 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.

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

6.2 Exclusion Criteria

1) Target Disease Exceptions

a) Systolic blood pressure (SBP) < 110 mm Hg at screening or pre-randomization

b) Heart rate < 50 beats per minute (bpm) or > 90 bpm at screening orpre-randomization

c) Permanent Atrial Fibrillation, Atrial Flutter or having Atrial Fibrillation, Atrial Flutter before start of the infusion

d) Permanent paced rhythm (VVI, DDD or BiV pacing)

e) NYHA Class IV symptoms of heart failure

2) Medical History and Concurrent Disease

a) Primary HF etiology attributable to either restrictive/obstructive cardiomyopathy, idiopathic hypertrophic or uncorrected severe valvular disease as defined by AHA/ACC/ESC criteria. (Note: A restrictive mitral inflow pattern is not exclusionary)

b) Pericardial tamponade or constrictive pericarditis

c) Large post-MI LV aneurisms

d) Intra-cardiac thrombus

e) Prior mitral valve repair, mitral or aortic prosthesis of any type.

f) LV assist device or prior heart transplant

g) Hospitalized for acute decompensated heart failure in the previous month

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

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

j) Considered clinically unstable for any condition

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

l) Liver disease defined as history of cirrhosis with evidence of portal hypertension such as varices, or encephalopathy, or total bilirubin > 3 mg/dL (> 51 μmol/L) or significant elevation of liver enzymes (AST, ALT > 3 times the upper limit of normal)

m) Prior solid organ transplant

3) Prior/Concomitant Therapy

a) Treatment with oral phosphodiesterase type 5 (PDE5) inhibitor sildenafil, vardenafil or avanafil within 24 hours of study drug infusion or treated with tadalafil within 4 days of study drug infusion

b) Treatment with intravenous inotropic therapy (dobutamine, milrinone, levosimendan) in the previous month or planned treatment in next 3 months.

c) Current treatment with chronic oral, transdermal or sublingual nitrates, except at the discretion of the investigator and treating physician, nitrates could be temporarily interrupted. In which case, an interruption of 3 days is required prior to start of study drug.

4) Physical and Laboratory Test Findings

a) Estimated glomerular filtration rate (eGFR) < 15 ml/min/1.73 m^2

b) 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)

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

5) Allergies and Adverse Drug Reaction

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

b) Allergic reactions to organic nitrates

6) 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, CXL-1427, or CXL-1020
e) Alcohol beverage consumption within 6 hours prior to randomization.
f) Low quality echocardiographic visualization windows and image acquisition
g) Body weight < 45 kg or ≥ 140 kg
h) Known hypersensitivity or contra-indication to the intravenous echocardiography contrast agent, in the event contrast echocardiography is used

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

6.3 Lifestyle Restrictions

Participants are not permitted to consume alcohol-containing beverages from midnight of the day before the treatment day until the day after the treatment day (Day 1 of each period).

6.4 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.

6.4.1 Retesting During Screening or Lead-In Period

Participant Re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a pre-randomization failure (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 2.-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified participants. Consultation

with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter could allow for the patient to be randomized.

7 TREATMENT

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

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP).

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, nitroglycerin, 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 is considered non-investigational product.

Study medication will be prepared by an unblinded pharmacist (or appropriate designee) in the Day 1 of each period (treatment day), at time of randomization in the first period and before start of the infusion for the subsequent 2 periods. 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 7.-1: Study treatments for CV013020

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-986231For Injection[a]	240 mg/vial	IP	Open Label	Vial(s) in a carton	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

Table 7.-1: Study treatments for CV013020

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
					characteristics
Nitroglycerin injection[c]	5 mg/mL (50 mg/10 mL Single Dose Vial or Ampoule)	IP	Open Label	Vial(s) or Ampoule(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).

[c] Nitroglycerin may be supplied by BMS centrally or through site sourcing procedures.

7.1 Treatments Administered

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

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
BMS-986231	3 µg/kg/min for 10 min (5 mL/H) 6 µg/kg/min for 10 min (10 mL/H) 12 µg/kg/min for the rest of the 5-hour infusion (20 mL/H)	Single infusion	IV
Nitroglycerin	20 µg/min for 10 min (5 mL/H) 40 µg/min for 10 min (10 mL/H) 80 µg/min for the rest of the 5-hour infusion (20 mL/H)	Single infusion	IV
Placebo*	5 mL/H for 10 min 10 mL/H) for 10 min 20 mL/H for the rest of the 5-hour infusion	Single infusion	IV

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

7.2 Method of Treatment Assignment

Study using Interactive Response Technology (IRT): All participants will be centrally randomized using an Interactive Response Technology (IRT). Before the study is initiated, each user will receive login information and directions on how to access the IRT.

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

Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with 00001, (e.g., 00001, 00002, 00003.... 00010). 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 6.4) will be assigned a new participant number.

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

7.3 Blinding

7.3.1 Emergency Unblinding

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

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

For this study, the method of unblinding for emergency purposes is via the Interactive Response Technology (IRT) system. For information on how to unblind in an emergency, consult the IRT manual.

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.

7.3.2 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 subject during the placebo treatment period. Likewise, the Biotransformation 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.

7.4 Dosage Modification

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 intravenous catheter, the pump should be set to deliver the rates of infusion indicated on the infusion bag label according to the up-titration schedule (See Section 5.1).

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 5−hours, or at the time of any early discontinuation, should be recorded in the clinic source documents.

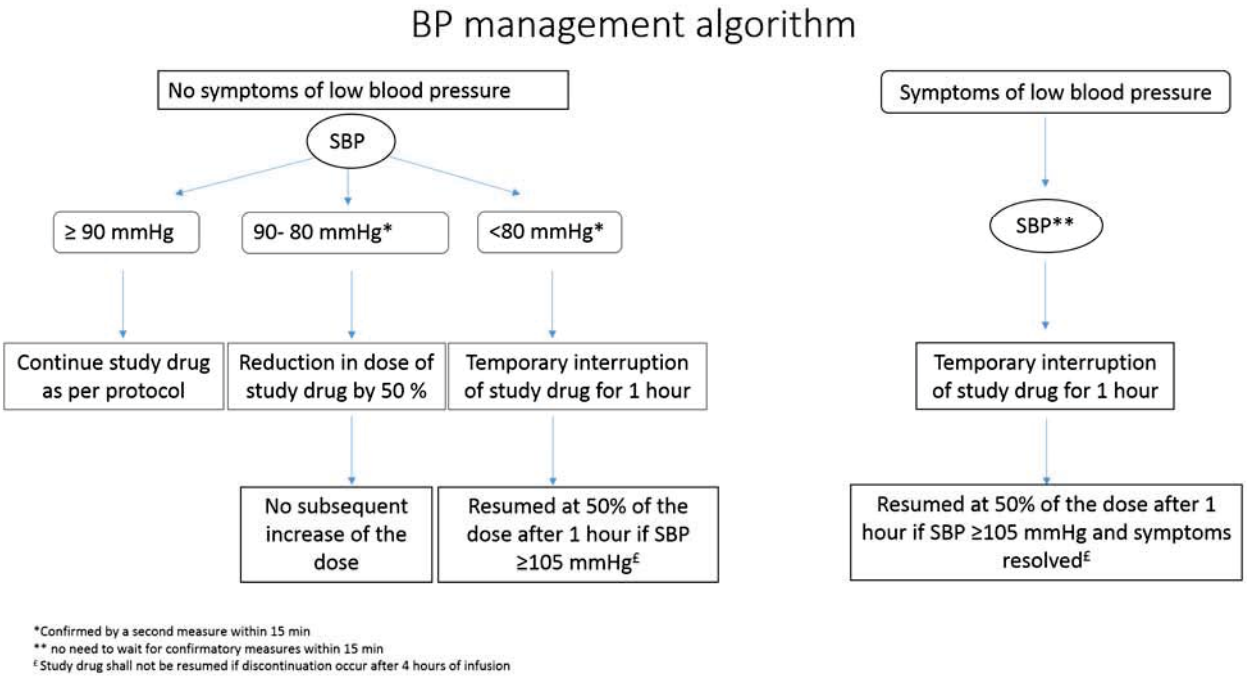
At any time during the administration of study drug, the study drug infusion must be discontinued if an adverse event or any other safety issue suggests it is not in the patient's best interest to continue to receive study drug.

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 7.4-1)

- **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 decreases to <80 mmHg or symptoms of low blood pressure occur within the first 4 hours of infusion. If the SBP is ≥ 105 mmHg after one hour interruption, the study drug could be resumed at 50 % of the dose to complete 5-hours of effective study drug infusion.
- **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 4 hours of infusion.

End of infusion procedures should be done as soon as possible after interruption or discontinuation of the study drug. If an infusion in a given period is discontinued, patients remain eligible to complete subsequent periods.

Figure 7.4-1: BP Management Algorithm



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.

In order to ensure compatibility with BMS-986231 and NTG, the placebo solution will be D5W.

7.5 Preparation/Handling/Storage/Accountability

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

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

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

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, storage temperatures, reconstitution, and use of required processes (e.g., required diluents, administration sets).

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

7.5.1 Retained Samples for Bioavailability / Bioequivalence

Not Applicable.

7.6 Treatment Compliance

Not applicable.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

- Initiation of PDE5 inhibitors is prohibited during study drug infusion and 24 hours after the end of the study drug.

- Administration of IV vasoactive drugs (such as dopamine, dobutamine, enoximone, nitroprusside, levosimendan or milrinone) is not permitted during study drug infusion
- Chronic oral heart failure medications (diuretics, ACE inhibitors, ARBs, MRA, beta-blockers, calcium antagonists) will be withheld in the morning of the treatment day and will be administered after the end of the study drug infusion
- Initiation of chronic oral, transdermal or sublingual nitrates is prohibited during the treatment period.

7.7.2 Other Restrictions and Precautions

Not applicable

7.7.2.1 Imaging Restriction and Precautions

Not applicable.

7.8 Treatment After the End of the Study

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

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information
- Any clinical adverse event (AE), laboratory abnormality or inter-current illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- If study medication has been interrupted for low blood pressure, resumed, and an episode of hypotension (or symptoms of hypotension) reoccurs

Refer to Section 2 the Schedule of Activities for data to be collected at the time of treatment discontinuation and follow-up, and for any further evaluations that can be completed

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In the event a normal healthy 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 (e.g., dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion among the investigator, the BMS 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 Section 9. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

8.1.1 Post Study Treatment Study Follow-up

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 9 until death or the conclusion of the study.

Participants who discontinue study treatment may continue to be followed.

8.2 Discontinuation from the Study

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

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

8.3 Lost to Follow-Up

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

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in Section 2 the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Section 2 Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in Section 2 the Schedule of Activities.

9.1 Efficacy Assessments

9.1.1 Imaging Assessment for the Study

Echocardiography

A central core lab will perform all echocardiographic analyses in this study. Sites should be trained prior to scanning the first study participant. Image acquisition guidelines and submission process will be outlined in the Imaging Manual to be provided by the core lab.

Prior to enrollment in the study, study participants will undergo a screening echocardiography that will be submitted to the core lab for review to confirm eligibility. It will assess the ejection fraction and the quality of echocardiography images and windows.

Contrast echocardiograms could be considered in selected patients to enhance image quality in those patients with poor endocardial definition. Contrast echocardiography should only be used if the sonographer and the investigative site meet the following conditions: are skilled in the administration of contrast agents and routinely use the technique in their clinical practice, are fully aware of the indications and contraindications for the use of contrast, are trained in the immediate recognition and management of adverse events, and have the necessary equipment, drugs, and supplies readily available for managing adverse events. For further details, please refer to the echo lab manual.

At least 2 echocardiograms will be performed on the first day of each period (prior to infusion and at the end of the infusion between hour 4 and hour 5 of the infusion). If the study drug is prematurely interrupted, a supplementary echocardiogram will be performed as soon as possible after interruption. If the study drug is resumed, another echocardiogram will be performed between hour 4 and hour 5 of the effective perfusion time.

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

Whole body bioimpedance

NICaS device will non-invasively assess cardiac output based on whole body bioimpedance; it has been demonstrated to meet FDA standards for bioequivalence when compared to thermodilution-based cardiac output methods[34].

Pulse wave analysis

Noninvasive central aortic pressure measurement and waveform analysis will be performed in this study at time-points indicated in Table 2.-2 (time and events schedule). Mean cardiac power will be calculated as the product of measured cardiac output (or index) and mean central aortic blood pressure[35].

9.2 Adverse Events

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

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

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

Contacts for SAE reporting specified in Appendix 3

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of non-serious AE information begins at initiation of study treatment until 24 hours after discontinuation of the infusion at the time-points specified in Section 2 the Schedule of Activities (Section 2). Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB)[33] represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

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

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

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

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

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

9.2.2 Method of Detecting AEs and SAEs

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

9.2.3 Follow-up of AEs and SAEs

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

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

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

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

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance

Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3

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

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

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

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

9.2.6 Laboratory Test Result Abnormalities

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

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any 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 (e.g., anemia versus low hemoglobin value).

9.2.7 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN) if baseline values are within the normal range, or > 2 times the baseline values in case of baseline values above the 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 AT elevation and hyperbilirubinemia, including, but not limited to, worsening heart failure, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) herbal medications or substances known to be hepatotoxic.

9.2.8 Other Safety Considerations

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

9.3 Overdose

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

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 intravenous 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 heart failure 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 heart failure subjects. If marked hypotension occurs, appropriate treatment, including intravenous pressor agents may be required to support blood pressure.

9.4 Safety

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

9.4.1 Physical Examinations

Refer to Section 2: Schedule of Activities.

9.4.2 Vital signs

Refer to Section 2: Schedule of Activities.

9.4.3 Electrocardiograms

Refer to Section 2: Schedule of Activities.

9.4.4 Clinical Safety Laboratory Assessments

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

Local laboratory assessments

The following local laboratory tests will be performed as part of the screening evaluation and in the morning of each treatment day. 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)
- Total Bilirubin
- 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 in each treatment period,).

Follicle stimulating hormone (FSH) (screening only for women only)

In 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/exclusion criteria.

- The study participant had a stable condition and didn't have any change in medication since the screening visit / previous period.

Central laboratory assessments

The following laboratory tests will be performed and submitted to the Central Laboratory for analysis as per the Study Assessment and Procedures

Hematology

- Hemoglobin
- Hematocrit
- White blood cell count, including differential
- Platelet count

Serum Chemistry

- Aspartate Aminotransferase (AST, SGOT)
- Alanine Aminotransferase (ALT, SGPT)
- Total bilirubin
- Direct bilirubin
- Alkaline phosphatase
- Lactate dehydrogenase (LDH)
- Serum Creatinine (Scr)
- Blood Urea Nitrogen (BUN)
- Uric acid
- Fasting glucose
- Total Protein
- Albumin
- Electrolytes
  - Sodium
  - Potassium
  - Chloride
  - Calcium
  - Phosphorus
  - Magnesium
- Creatine kinase (Creatine Phosphokinase) (CK) (CPK)
- Biomarkers: cystatin C, N-Gal

Urinalysis

- Protein
- Glucose
- Blood
- Leukocyte esterase

- Specific gravity
- pH
- Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick

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

9.4.5 Suicidal Risk Monitoring

Not applicable

9.4.6 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 Study Investigator as per standard medical/clinical judgment.

9.5 Pharmacokinetic Assessments

Blood samples will be collected for pharmacokinetic assessments as described in Table 9.5-1.

Table 9.5-1: Pharmacokinetic Assessments

Study Day of Sample Collection	Event	Time (Relative To Dose) Hour: Min	Blood Sample
1	Pre-dose	00:00	x
1	0.5 hour (± 15min)	00:30	x
1	1 hour (± 30min)	01:00	x
1	4.5 hours* (± 30min)	04:30	x
1	7 hours (± 30min)	07:00	x
1	Dose lowered due to safety event (± 30min)	Misc.	x
1	Early Discontinuation	Misc.	x

**end of the infusion sample should be taken as close to the end of the infusion as possible*

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.

Blood samples will be collected from all subjects at pre-dose, 0.5, 1 and 4.5 hours during infusion and 2 hours after end of infusion and plasma concentrations will be measured using LC-MS.

9.6 Pharmacodynamics

Not applicable.

9.7 Pharmacogenomics

9.7.1 ADME Sampling

A 6-mL whole blood sample will be drawn at baseline (Day 1, as indicated in Section 2 Schedule of Activities) for potential analysis of DNA variants in genes solely related to disposition of BMS-986231 (Drug absorption, distribution, metabolism, and excretion (ADME) related genes such as mARC, CYP, uridine 5'-diphospho-glucuronosyltransferase (UGT), reducing and hydrolytic enzymes and drug transporters), except where prohibited by local laws or regulations. Investigation of polymorphisms in ADME genes will only be conducted in the event that variable PK is observed. Further details of blood collection and processing will be provided to the site in the procedure manual.

[redacted]

[redacted]

[redacted] [redacted]

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

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9.9 Health Economics OR Medical Resource Utilization and Health Economics

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

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

Based on a review of stroke volumes and stroke volume indices from the literature[36,37], baseline stroke volume index generally ranged from 30-40 mL/m², with inter-individual SD of approximately 25 – 35% of the mean. Likewise, SV values generally ranged from 50-70 mL, with inter-individual SD of approximately 25 – 35% of the mean. Results from these studies also suggest intra-individual correlations in the range of 0.6 – 0.8.

Sample size calculations assume baseline SVI of approximately 30 mL/m², with placebo values consistent with baseline, an increase of 15% from baseline, relative to placebo, as meaningful (e.g. 4.5 mL/m²), an inter-individual SD of 10 mL/m², and intra-individual correlations for the difference between placebo and HNO of 0.7. Using these assumptions, approximately 36 subjects with data from treatment periods being compared will be required to achieve a power of 90%, with a type I error probability of 0.05 (2-sided). In order to address the potential for missing data arising from dropout, an allowance of 15% subjects will be included, with a resulting target sample size of 42 subjects to be randomized. Sample sizes are calculated based on method IV from Mehrotra[38], which compares post baseline values, adjusting for the differences in the baseline value.

10.2 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.
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.

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary and secondary endpoints. For analyses involving baseline, the baseline value is defined by the last value prior to the start of infusion for a specified period, unless otherwise noted.

10.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Stroke volume index derived from the left ventricular outflow tract (LVOT) Doppler echocardiogram will be assessed using a contrast comparing placebo and BMS-986231 from a mixed model repeated measures (MMRM) analysis, with sequence, treatment period, and treatment, and the difference in the treatment period baselines as a covariate[39]. The Kenward-Roger approximation for the degrees of freedom will be specified for the model. Estimation of the variance covariance will be based on unstructured (UN) R matrix assuming no common variances or covariances.
Secondary	Analyses of secondary endpoints will use a similar model as for the primary endpoints. For comparisons with NTG, the contrast and covariates will refer to values from the treatment periods using NTG and BMS-986231. No adjustments will be made for multiple comparisons.

10.3.2 Safety Analyses

All safety analyses will be performed on the Safety Population (see Section 10.2).

For safety analyses, all recorded adverse events 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.

10.3.3 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. DNA variants in genes related to mARC and in ADME related genes will be performed if extensive between-subject variability in exposure of BMS-986231 is observed. Results may be reported in a separate report.

10.3.4 Pharmacokinetic Analyses

Pharmacokinetic parameters for BMS-986231 and BMT-284730 and other metabolites (eg, BMT-279554 & CAR-000463) will be estimated as appropriate. The plasma concentration may also be used to conduct population pharmacokinetic analysis and exposure-response analysis with select efficacy and safety endpoints. Results of the population pharmacokinetic and exposure-response analysis will be reported in a separate report.

10.3.5 Interim Analyses

Not applicable.

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
A-wave	A-wave late active filling of LV
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
ALT	alanine aminotransferase
AR	additional research
ARB	angiotensin receptor blockers
ARNI	angiotensin-receptor/neprilysin inhibitor
AST	aspartate aminotransferase
BiV	biventricular
BMS	Bristol-Myers Squibb
BNP	brain natriuretic peptide
BPM	beats per minute
BUN	blood urea nitrogen
CHF	congestive heart failure
CI	cardiac index
CRF	case report form
CRP	C-reactive protein
CVA	cerebrovascular accident
D5W	5% dextrose in water
DBP	diastolic blood pressure
DDD	pacemaker dual chamber pacing and sensing, both triggered and inhibited mode
DILI	drug induced liver injury
DNA	deoxyribonucleic acid
DT	deceleration time
DTI	doppler tissue imaging
ECG	electrocardiogram
EDPVR	end-diastolic pressure volume relationship
EDT	E-wave deceleration time
eGFR	estimated glomerular filtration rate
ER	exposure-response
ESC	European Society of Cardiology
ESPVR	end systolic pressure-volume relationship
E-wave	E-wave early passive filling of the left ventricle
FDA	Food and Drug Administration

Term	Definition
FSH	follicle stimulating hormone
GLS	global longitudinal strain
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HNO	Nitroxyl, Nitrosyl Hydride, or hydrogen Oxonitrate
HR	heart rate
IB	investigator brochure
IEC	independent ethics committee
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
ITT	intent to treat
IV	intravenous
IVRT	isovolumetric relaxation time
K+	Potassium
LA	left atrium
LC-MS	liquid chromatography–mass spectrometry
LDH	lactate dehydrogenase
LV	left ventricle
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
MAP	mean arterial pressure
mARC	mitochondrial amidoxime-reducing component
MI	myocardial infarction
MMRM	mixed model repeated measures
MRA	mineralocorticoid receptor antagonists
Na+	Sodium
NCV	nerve conduction velocities
NICaS	non invasive cardiac system
NO	nitric oxide
NTG	nitroglycerin
NT-pro BNP	N terminal- pro BNP
NYHA	New York Heart Association
PADP	pulmonary artery diastolic pressure
PCWP	pulmonary capillary wedge pressure
PDE5	phosphodiesterase type 5
pH	potential of hydrogen
PK	pharmacokinetic
PRSW	preload recruitable stroke work
RA	right atrium

Term	Definition
RAP	right atrial pressure
RNA	ribonucleic acid
RTR2	ryanodine receptor 2
RV	right ventricle
SAE	serious adverse event
SBP	systolic blood pressure
Scr	serum creatinine
SD	standard deviation
sGC	soluble guanylate cyclase
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
STE	speckle-tracking echocardiography
SUSAR	suspected, unexpected serious adverse reaction
SVI	stroke volume index
TAPSE	tricuspid annular plane systolic excursion
TIA	transient ischemic attack
TR	tricuspid regurgitation
ULN	upper limit of normal
VTI	velocity time integral
VVI	pacemaker single chamber, ventricular pacing in the inhibited mode
WOCBP	women of child bearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP),
- as defined by the International Council on 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 breach of the conditions and principles of Good Clinical Practice (GCP) (occurring in any country) in connection with that trial or the protocol related to the trial which is likely to affect to a significant degree the safety or physical or mental integrity of 1 or more subjects of the trial or the scientific value of the trial.

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

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

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

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

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

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

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

SOURCE DOCUMENTS

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

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

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

STUDY TREATMENT RECORDS

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

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

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

CASE REPORT FORMS

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

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used.

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

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

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. 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

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

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

RETURN OF STUDY TREATMENT

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

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

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

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.

- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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

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

CLINICAL STUDY REPORT AND PUBLICATIONS

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

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:
An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. 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 verbatim term.
Events <u>NOT</u> Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 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 9.2.5 for reporting pregnancies).

EVALUATING AES AND SAES

Assessment of Causality

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

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the eCRF.
  - The paper SAE Report Form is only intended as a back-up option when the electronic data capture (EDC) system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile (fax) transmission
    - When paper forms are used, the original paper forms are to remain on site
- Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

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

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

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 1 days 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 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 intrauterine devices (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

*** REFERENCES FOR THE USE OF CONDOMS WITH SPERMICIDE.**

Kestelman P. et. al., Efficacy of the Simultaneous Use of Condoms and Spermicides Family Planning Perspectives.Vol 23 (5); October 1991.
Gabbay MB, Thomas J, Gibbs A, Hold P. A Randomized Crossover Trial of The Impact of Additional Spermicide on Condom Failure Rates. Sex Transm Dis 2008; 35: 862-8.

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

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

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until the end of relevant systemic exposure defined as 91 days after the end of treatment in the male participant.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 91 days after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 91 days after the end of treatment.
- Refrain from donating sperm for the duration of the study treatment and for 91 days after the end of treatment.

COLLECTION OF PREGNANCY INFORMATION

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