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Clinical Protocol CV013011

A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Dose-Ranging, Phase 2b Study of the Safety and Efficacy of Continuous 48-Hour Intravenous Infusions of BMS-986231 in Hospitalized Patients with Heart Failure and Impaired Systolic Function

Revised Protocol 02

Study Director

[redacted]

Medical Monitor

Maria Borentain MD

[redacted]

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 02	09-Apr-2018	Expansion of screening period, addition of Holter Monitoring in a subset of patients, addition of Actigraphy monitoring in a subset of patients, and clarifications throughout the document.
Administrative Letter 02	05-Dec-2017	Clarifies secondary packaging of BMS986-231 as a carton containing 5 or 6 vials.
Administrative Letter 01	14-Feb-2017	Administrative clarifications throughout the protocol.
Revised Protocol 01	11-Oct-2016	Incorporates changes from Amendment 01.
Amendment 01	11-Oct-2016	Addition of two unblinded interim analysis, addition of Sensory Motor Survey, clarification and updates to Eligibility criteria, and additional edits throughout the document to improve readability.
Original Protocol	28-Jun-2016	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 02:

These changes serve to clarify procedures for Part II Cohort 2 of the study. Part I Cohort 1 of the study is not impacted. Changes include:

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.3.2 Exclusion Criteria	Exclusion criteria # 2b was modified to clarify: Suspected acute lung disease (eg, pneumonia or asthma) or severe chronic lung disease (eg, severe chronic obstructive pulmonary disease, pulmonary fibrosis, patients with hypercapnia or requiring home oxygen therapy or chronic oral steroids.)	Additional clarification for exclusion of patients with severe lung disease.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.1 Study Design and Duration	Changed to: Study Medication infusion must start within 18 hours of presentation (or 48 hours in Part II Cohort 2 of the trial), with presentation defined as the first dose of diuretic for current episode	[redacted]
Section 5.1.2 Treatment and In-Hospital Follow-up	Addition of window to collect vital signs within .25 hours of specified time points.	[redacted]
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized

SYNOPSIS

Clinical Protocol CV013011

Protocol Title: A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Dose-Ranging, Phase 2b Study of the Safety and Efficacy of Continuous 48-Hour Intravenous Infusions of BMS-986231 in Hospitalized Patients with Heart Failure and Impaired Systolic Function

Investigational Products, Dose and Mode of Administration, Duration of Treatment with Investigational Products: The investigational medicinal product is a solution for IV infusion containing BMS-986231 drug product (reconstituted in sterile water for injection), 5% dextrose (glucose) in water for injection (D5W) and potassium acetate (to achieve a 10 mM concentration of potassium acetate).

Study Phase: Phase 2B

Purpose: The purpose of this study is to evaluate the safety, tolerability, and efficacy of BMS-986231in subjects with heart failure (HF) and reduced systolic function (LVEF < 40%) who are admitted to the hospital with signs and symptoms of acute decompensated heart failure (ADHF).

Research Hypothesis: BMS-986231 is safe and tolerated with regard to clinically relevant hypotension compared with placebo in hospitalized heart failure with reduced ejection fraction (HFrEF) subjects with ADHF.

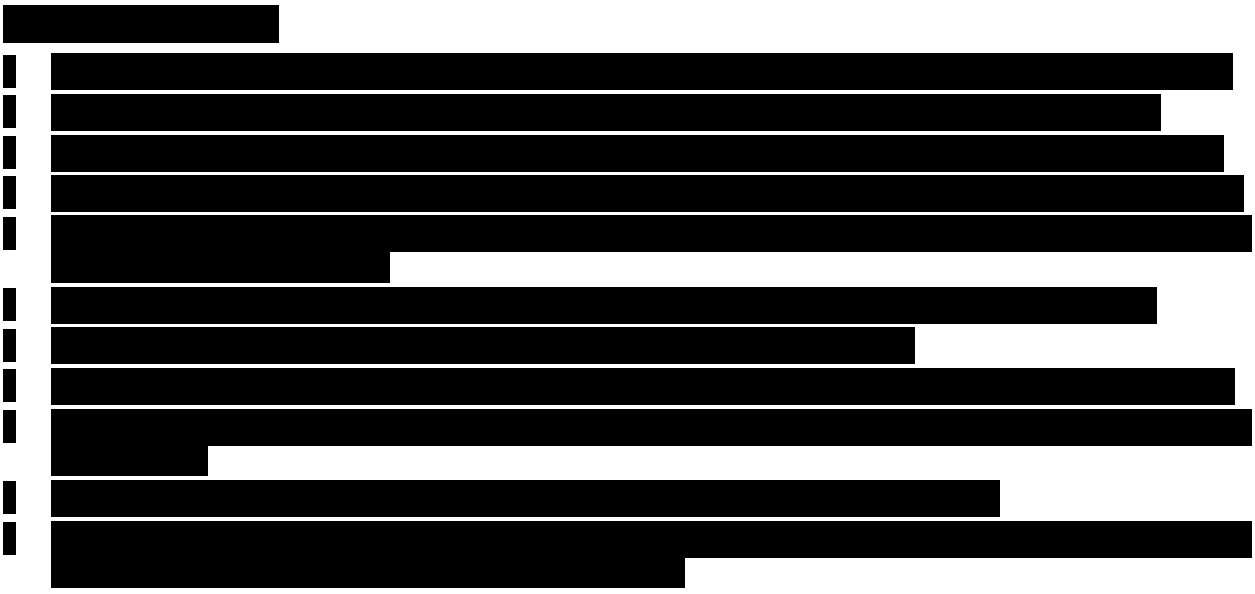
Objectives:

Primary Objective:

The primary objective is to evaluate the effects of various doses of BMS-986231 compared to placebo on clinically relevant hypotension (defined by SBP < 90 mm Hg or symptoms of hypotension)

Secondary Objectives:

- Assess the effect of BMS-986231 on NT-proBNP
- Assess the effect of BMS-986231 on patient-reported resting dyspnea as measured by the 11-point Numerical Rating Scale (NRS)



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Safety Objectives:

- Evaluate the effect of BMS-986231 on incidence of symptomatic hypotension
- Evaluate the effects of BMS-986231 on the incidence of SBP < 90 mm Hg.
- Evaluate the incidence of dose reductions, temporary interruptions, and permanent discontinuation of BMS-98623 infusions
- Evaluate the safety and tolerability of a continuous 48-hour infusion of BMS-986231 in hospitalized HFrEF subjects with ADHF
- Evaluate the effect of BMS-986231 on high sensitivity (Hs) Troponin T
- Assess the effect of BMS-986231 on mortality at Day 182

Study Design: This is a multi-center, randomized, placebo-controlled, double-blind study of continuous 48-hour intravenous (IV) infusions of BMS-986231 in hospitalized HFrEF subjects with ADHF. The trial was designed to identify the doses of BMS-986231 that are safe and tolerated with regard to clinically relevant hypotension.

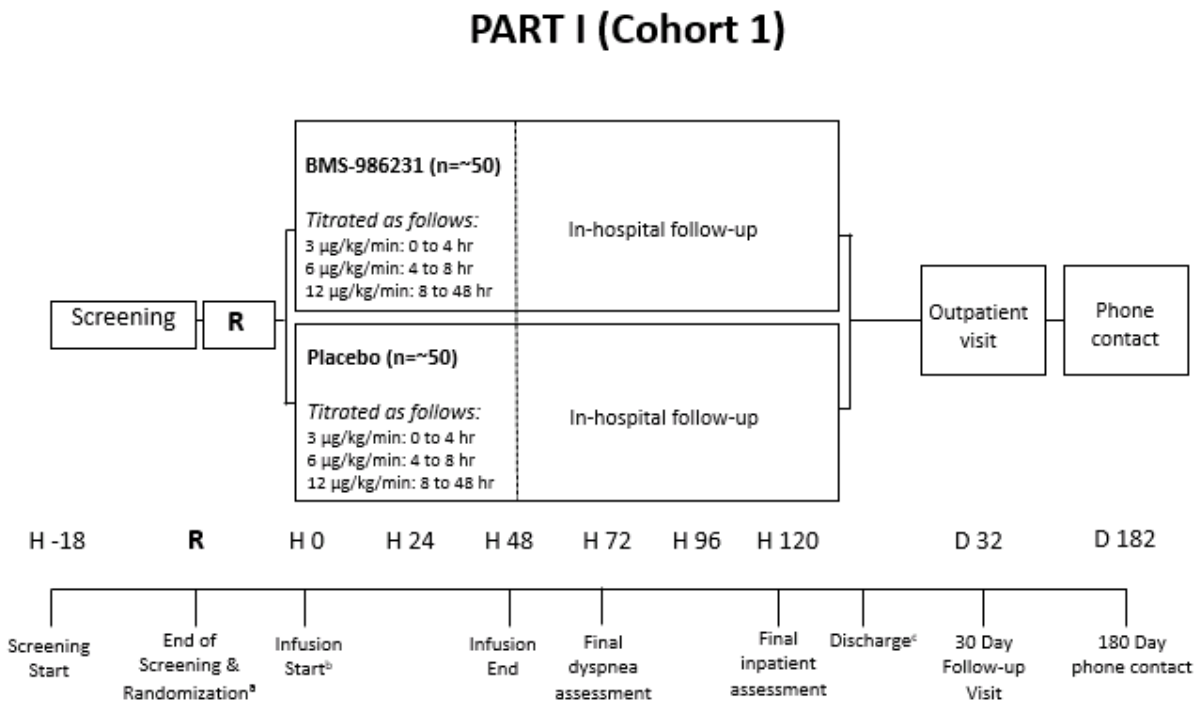
The study consists of 2 parts, each with a unique cohort of subjects.

Patients that are randomized in Part I of the study will not be allowed to participate in Part II.

In Part I (Cohort 1) of the study, approximately 100 subjects will be randomized in a 1:1 ratio to placebo or an escalating dose of BMS-986231 (3 μg/kg/min for 4 hours, then 6 μg/kg/min for another 4 hours, then 12 μg/kg/min for the remaining 40 hours).

In Part II (Cohort 2) of the study, the 2 highest planned doses of BMS-986231 in Cohort 1, BMS-986231 6 μg/kg/min and BMS-986231 12 μg/kg/min, will be administered. Approximately 210 subjects will be randomized in a 1:1:1 ratio to one of the 2 active doses of BMS-986231 or placebo. If BMS-986231 12 μg/kg/min is not considered to be a tolerated dose in Part I, then BMS-986231 3 μg/kg/min and BMS-986231 6 μg/kg/min will be evaluated in Part II. In the event that neither 6 μg/kg/min nor 12 μg/kg/min are tolerated, the protocol will require modification.

Study Schematic:

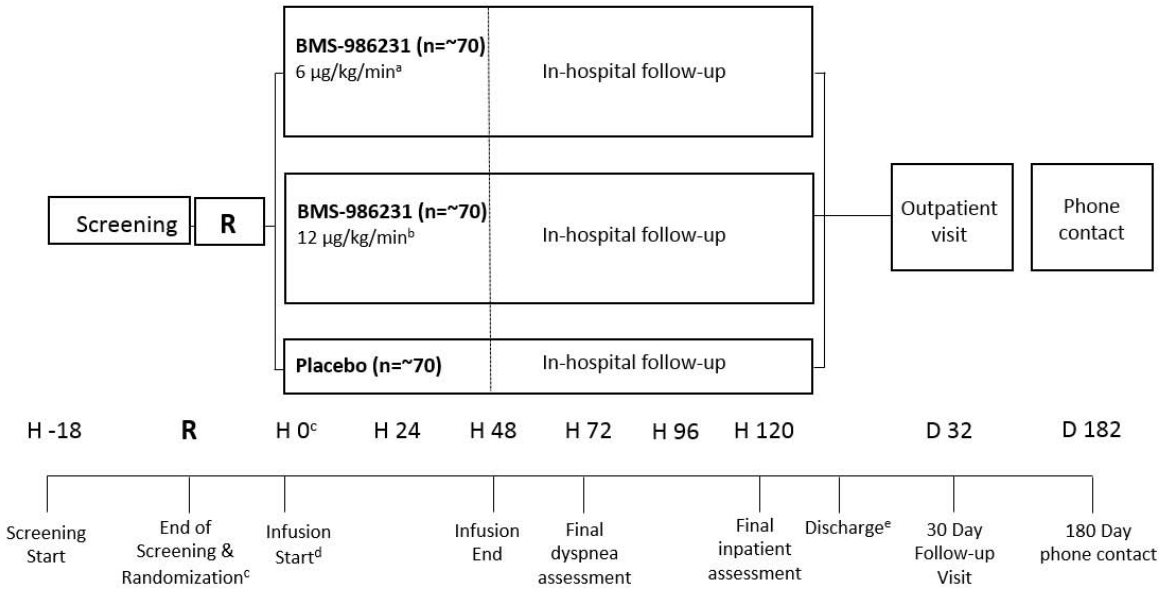


[a] Every effort should be made to initiate study drug administration promptly after randomization

[b] Study Medication infusion must start within 18 hours of presentation (or 48 hours in Part II Cohort 2 of the trial), defined as the first dose of diuretic for current episode, but not within 2 hours after an IV bolus dose of intravenous diuretics, or within 2 hours after the initiation or an increase in the dose of an IV diuretic administered by continuous infusion

[c] Discharge may occur as per standard medical practice. It is recommended that subjects remain in the hospital for at least 24 hours after the completion of the 48-hour infusion of study drug for safety monitoring

PART II (Cohort 2)



[a] 3 µg/kg/min if 12 µg/kg/min is not tolerated in Part I

[b] 6 µg/kg/min if 12 µg/kg/min is not tolerated in Part I

[c] Every effort should be made to initiate study drug administration promptly after randomization

[d] Study Medication infusion must start within 18 hours of presentation, (or 48 hours in Part II Cohort 2 of the trial) defined as the first dose of diuretic for current episode, but not within 2 hours after an IV bolus dose of intravenous diuretics, or within 2 hours after the initiation or an increase in the dose of an IV diuretic administered by continuous infusion

[e] Discharge may occur as per standard medical practice. It is recommended that subjects remain in the hospital for at least 24 hours after the completion of the 48-hour infusion of study drug for safety monitoring.

Study Population:

Key Inclusion Criteria:

- Males and Females, at least age 18 (or age of majority)
- Subjects being hospitalized for ADHF
- Have had at least 40 mg furosemide intravenous, or equivalent, (eg, 40 mg furosemide equivalent to 20 mg torsemide or to 1 mg bumetamide) for the current ADHF episode
- Subject must be randomized and treated within 18 hours of first dose of intravenous diuretic for Part I Cohort 1 (or 48 hours of first dose for Part II Cohort 2).
- Have dyspnea at rest or with minimal exertion after administration of at least 1 dose of intravenous diuretics. Subject must not be randomized within 2 hours after an IV bolus dose of intravenous diuretics, or within 2 hours after the initiation or a dose increase of an IV diuretic administered by continuous infusion
- Have a history of heart failure and a left ventricular ejection fraction (LVEF) $\leq 40\%$, as assessed by echocardiography, a multigated acquisition (MUGA) scan or magnetic resonance imaging (MRI) scan
  - Note: Ejection fraction documentation up to 18 months prior to screening may be used if there is no clinical expectation of improvement in ejection fraction in that timeframe (eg, the patient has not had biventricular pacing initiated during that period)
- Have at least 2 of the following at time of screening:
  - evidence for pulmonary congestion on chest x-ray
  - rales by chest auscultation
  - edema $\geq$ 2+ on a 0 to 3+ scale (easily identifiable indentation, skin rebounds in 15-30 seconds)
  - presence of jugular venous distention
- Have an elevated NT-proBNP $\geq$ 1600 pg/mL (189 pmol/L) or BNP $\geq$ 400 pg/mL (116 pmol/L) as determined at the local laboratory within 18 hours prior to the start of study drug infusion for Part I Cohort 1 (or 48 hours for Part II Cohort 2)
- For subjects with atrial fibrillation: NT-proBNP $\geq$ 2400 pg/ml or BNP $\geq$ 600 pg/ml
- Body weight $\geq$ 50 kg and < 140 kg at screening
- Women of childbearing potential must have negative serum or urine pregnancy test within 18 hours of start of drug for Part I Cohort 1 (or 48 hours for Part II Cohort 2)

Key Exclusion Criteria:

- Screening OR baseline systolic blood pressure (SBP) of <105mm Hg or >160mm Hg at screening and just prior to randomization
- Heart rate < 50 or >130 beats per minute (bpm) at screening and just prior to randomization
- Have 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: Functional mitral regurgitation, as well as restrictive mitral inflow pattern on echocardiography is not exclusionary
- Have a body temperature $\geq$ 38.5°C (101.3°F) at any time from screening to randomization
- Have an active infection requiring current IV anti-microbial treatment
- Considered clinically unstable for other conditions than acute heart failure, either because of acute coronary syndrome or ongoing arrhythmia (or be receiving concomitant parenteral therapy with any antiarrhythmic drugs), or other unstable non-cardiovascular disease
- Suspected acute lung disease (e.g. pneumonia or asthma) or severe chronic lung disease (e.g. severe chronic obstructive pulmonary disease, pulmonary fibrosis, patients with hypercapnia or requiring home oxygen therapy or chronic oral steroids.)
- Have a history of sudden cardiac death with resuscitation within the past 6 months

- Be 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
- Serious comorbid non-cardiovascular disease in which the life expectancy of the subject is < 6 months (eg, acute systemic infection – sepsis, metastatic cancer, or other serious illnesses)
- Severe 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)
- Prior cardiac or renal transplant
- Have persistent abnormal serum electrolytes not resolved before randomization, 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)
- Have severe renal insufficiency before randomization (and during the current hospitalization) defined as an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 [based on any standard limit and equation employed by the local lab, eg, Modification of Diet in Renal Disease (MDRD) equation]. For patients with eGFR values less than but close to 30 mL/min/1.73m^2 upon testing, retesting is allowed
- Subjects administered IV or transdermal nitrate therapy prior to randomization, except if all 3 of the following criteria are met:
  - Systolic blood pressure at screening or just prior to randomization is > 120 mm Hg AND
  - The IV nitroglycerin dose is < 100 µg/min (or isosorbide dinitrate < 3 mg/hour), AND
  - The infusion rate and dose has been unchanged for > 2 hours
- History of chronic or intermittent renal support therapy (hemodialysis, ultrafiltration, or peritoneal dialysis)
- Subjects treated during the current hospitalization with IV vasoactive drugs such as dopamine, dobutamine, enoximone, nesiritide, nitroprusside, levosimendan, amrinone , milrinone, carperitide or nicorandil prior to start of study drug infusion, or have an anticipated need to be treated with any of these agents during the study drug infusion
- Subjects receiving any mechanical ventilation at the time of screening
- Subjects receiving non-invasive ventilation (CPAP/BiPAP) < 2 hours prior to randomization
- Participation in an investigational clinical drug study within 30 days or 5 elimination half-lives, (whichever is longer) prior to randomization

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

Study Drug for CV013011		
Medication	**Potency**	**IP/Non-IP**
BMS-98623 For Injection	BMS-986231 240 mg/vial	IP
Potassium Acetate	2 mEq/mL (20mL/vial)	Non-IP

BMS will provide Investigational drug product BMS-986231 for infusion (active pharmaceutical ingredient BMS-986231 formulated with Captisol® 3405 mg/vial) to all sites. In addition, Potassium acetate is to be locally sourced by sites within the US and will be supplied to all ex-US sites.

Study Assessments:

Blood pressure assessment:

The primary endpoint of the study is the incidence of clinically relevant hypotension, defined by SBP < 90 mm Hg (confirmed by a repeated value < 90 mm Hg) or symptoms of hypotension, up to 6 hours after the end of study drug infusion. Thus hypotension will be assessed by collection of symptoms and blood pressure measurements.

Symptomatic hypotension is defined as the presence of both low SBP and symptoms (eg, lightheadedness, dizziness, etc.) due to low blood pressure.

Blood pressure measurements should be performed with the subject in a semi-recumbent (about a 30º angle) position, whenever possible.

Blood pressure will be measured as indicated in Table 5.1-2. In addition, sites may perform measurements at intervals defined by institutional standard of care for subjects receiving vasodilators, but no less than what is described in Table 5.1-2.

If the study drug dose is modified (decreased, interrupted, resumed or discontinued), the frequency of blood pressure measurements will follow a more intensive schedule for up to 6 hours following the dose modification (see table below). Upon completion of the intensive schedule, measurements can be either resumed per the original schedule, or follow the discontinuation schedule if the drug is permanently discontinued.

Schedule of Blood Pressure Collection Following a Dose Modification

	30 minutes Post	**1 hour post**	**2 hours post**	**4 hours post**	**6 hours post**
Dose reduction	X	X	X	X	X
Dose interruption	X	X	X	X	
Dose resumption	X	X	X	X	X
Dose discontinuation	X	X	X	X	X

Details for management of low blood pressure are detailed in section 5.3.1

In addition to assessments of blood pressure, the Investigator will be asked to collect and assess signs and symptoms of low blood pressure.

Efficacy Outcome Measures: Efficacy assessments will include the following:

Patient assessments of dyspnea severity at rest as measured by the 11-point Numerical Rating Scale (NRS) scores at screening and at 0, 6, 12, 24, 48, 72, and 120 hours after the start of study drug infusion.

Patient assessments of dyspnea severity at rest, using the 7-point Likert scale at 6, 12, 24, 48, 72, and 120 hours after the start of study drug infusion.

Patient assessments of global clinical status using the 7-point Likert scale at 6, 12, 24, 48, 72, and 120 hours after the start of study drug infusion.

An investigator assessment of in-hospital worsening heart failure since the start of the study drug infusion based on signs and symptoms of worsening heart failure along with the need for initiation or intensification of intravenous treatment for heart failure such as diuretics, vasodilators, inotropes, and mechanical support (mechanical ventilation, circulatory support, ultrafiltration or hemodialysis), as indicators of worsening heart failure, will be made at Hours 24, 48, 72, 96, and 120 or discharge, whichever comes first.

Mortality Measures:

Investigators will follow all subjects to Day 182 for mortality.

Investigators will be asked to report deaths and categorize them as either cardiovascular or non-cardiovascular death. All deaths will be assumed to be cardiovascular unless a non-cardiovascular cause can be clearly provided. Below is guidance for Investigator classification:

Cardiovascular Death:

Cardiovascular death includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes.

Non-cardiovascular Death:

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

Statistical considerations

Sample size:

For Part I (Cohort 1), approximately 50 subjects per group will be randomized to placebo or an incremental dose of BMS-986231 (3 - 6 - 12 μg/kg/min). Under a sample decision rule (eg, observed doubling with more than a 4% difference) and assuming clinically relevant hypotension incidences of 5% or 10% in the placebo group, the posterior probabilities of detecting an increase of 4-fold or 3-fold in incidence, respectively, are 86% and 80%, respectively. If there is no increase in clinically relevant hypotension, then the posterior probabilities of falsely detecting an increase are 11-12%.

For Part II (Cohort 2), approximately 70 subjects per group will be randomized to placebo or one of the two active dose levels of BMS-986231. Under a sample decision rule (eg, observed 1.8-fold increase with more than a 3% difference) and assuming clinically relevant hypotension incidences of 5% or 10% in the placebo group, the posterior probabilities of detecting an increase of 3-fold or 2.5-fold in incidence, respectively, are 82% and 80%, respectively. If there is no increase in clinically relevant hypotension, then the posterior probabilities of falsely detecting an increase are 13-15%. These probabilities do not reflect multiple comparison.

With regards to overall performance for selection of a maximally tolerated dose, a sample size of 50 per group for Part I (Cohort 1), along with 70 per group for Part II (Cohort 2) will identify a maximally tolerated dose approximately 50-70%, based on detecting an increase of 3-fold or 2.5-fold in incidence, and using sample decision rules that are consistent with above. Also, the design will provide an option to select a titrated 12 μg/kg/min dose approximately 60% of the time when that dose is tolerated, but a non-titrated 12 μg/kg/min dose is not tolerated. Conversely, the study design will not identify a maximally tolerated dose from Part II (Cohort 2) approximately 80%-85% of the time when no maximally tolerated dose exists.

Endpoints:

Primary Endpoint:

The primary endpoint is the incidence of clinically relevant hypotension, defined by SBP < 90 mm Hg (confirmed by a repeated value < 90 mm Hg) or symptoms of hypotension, up to 6 hours after the end of study drug infusion.

Secondary Endpoints:

- Change in NT-proBNP from baseline to Hour 24, 48, 72, 120 or discharge, whichever comes first, and at Day 32
- Change in patient-reported resting dyspnea from baseline through Hour 72, as measured by the area under the curve (AUC) of the 11-point Numerical Rating Scale (NRS) obtained at baseline, and Hours 6, 12, 24, 48, and 72

[redacted]

Safety Endpoints

- The incidence of symptomatic hypotension up to 6 hours after the end of study drug infusion
- The incidence of SBP < 90 mm Hg (confirmed by a repeated value)
- Change in Troponin T from baseline to Hour 24, 48, and 72
- Percentage of subjects who have died (all- cause and CV related) through Day 182

Additionally, the percentage of subjects with discontinuation due to symptomatic hypotension, as well as percentage of subjects with down-titrations, interruptions or discontinuations as a result of low blood pressure, either protocol specified clinically relevant hypotension, or asymptomatic decreases will be assessed. . Other safety endpoints include the incidence of Adverse Events and Marked Laboratory Abnormalities, changes from baseline in vital signs, ECGs, physical measurements and laboratory assessments through Hour 120 or discharge, whichever comes first. The incidence of Serious Adverse Events will be assessed though Day 32.

Analyses: Results from Part I (Cohort 1) and Part II (Cohort 2) will be presented separately.

For analyses involving baseline, the baseline value is defined by the last value prior to the start of infusion, unless otherwise noted.

Primary Endpoint Analysis

The incidence of clinically relevant hypotension from the start to 6 hours after the end of study drug infusion will be summarized by treatment. Point estimates and 95% CIs for event rates will be presented by treatment, together with point estimates and 95% CIs for the risk difference and relative risk between each BMS-986231 arm and placebo.

Secondary Endpoint Analyses

NT-proBNP will be summarized descriptively by treatment for each time point, as well as change from baseline.

Analyses for changes from baseline in the resting dyspnea as measured by the 11-point NRS will be done using a longitudinal repeated measures model, with baseline value and region as covariates. A trapezoidal rule will be applied to calculate AUC using model-estimated values from the time points. Missing values for the dyspnea NRS will not be imputed, except if a NRS cannot be obtained because the subject has died or is physically unable to complete the form. In these cases, a worst score imputation will be used for that time point.

[redacted]

[redacted].

Safety Endpoint Analyses

Troponin T will be summarized descriptively by treatment for each time point, as well as change from baseline.

Percentage of subjects who have died (all- cause and CV related) through Day 182 will be summarized descriptively by treatment.

All recorded adverse events 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.

Percentage of subjects with discontinuations due to symptomatic hypotension, as well as percentage of subjects with down-titrations or interruptions or discontinuations as a result of hypotension, either protocol specified clinically relevant hypotension, or asymptomatic decreases will be summarized descriptively by treatment.

In addition, the final infusion dose at the completion of 48 hours infusion will be summarized descriptively by treatment. The subjects who discontinued prematurely from infusion would be counted as having a final infusion dose of 0 μg/kg/min.

Cardiodynamic ECG assessment (Subset of Subjects in Part II Cohort 2 only):

The analysis will be based on exposure-response modeling of the relationship between plasma concentrations of prodrug BMS-986231, its byproduct BMT-284730 and other metabolites (eg, BMT-279554 & CAR-000463) and change-from-baseline QTcF (ΔQTcF) with the intent to exclude an effect > 10 msec at clinically relevant plasma levels.

In addition, the effect of BMS-986231 on the placebo-corrected ΔQTcF (ΔΔQTcF) will be evaluated at each post-dosing time point ('by-time point' analysis) using the Intersection Union Test. An analysis of categorical outliers will be performed for changes in heart rate (HR), PR, QRS, QTcF, T-wave morphology and U-wave presence

Pharmacokinetic Analyses

Blood samples will be collected from all subjects at 0.75, 4, 8, 14, and 48 hours during infusion and 4 hours after end of infusion and plasma concentrations will be measured using LC-MS. 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.

TABLE OF CONTENTS

1.2 Research Hypothesis

BMS-986231 is safe and tolerated with regard to clinically relevant hypotension compared with placebo in hospitalized heart failure with reduced ejection fraction (HFrEF) subjects with ADHF.

1.3 Objectives

1.3.1 Primary Objective

The primary objective is to evaluate the effects of various doses of BMS-986231 compared to placebo on clinically relevant hypotension (defined by SBP < 90 mm Hg or symptoms of hypotension).

1.3.2 Secondary Objectives

- Assess the effect of BMS-986231 on NT-proBNP
- Assess the effect of BMS-986231 on patient-reported resting dyspnea as measured by the 11-point NRS)

[redacted]

1.3.4 Safety Objectives

- Evaluate the effect of BMS-986231 on incidence of symptomatic hypotension
- Evaluate the effects of BMS-986231 on the incidence of SBP < 90 mm Hg.
- Evaluate the incidence of dose reductions, temporary interruptions, and permanent discontinuation of BMS-98623 infusions.
- Evaluate the safety and tolerability of a continuous 48-hour infusion of BMS-986231 in hospitalized HFrEF subjects with ADHF
- Evaluate the effect of BMS-986231 on high sensitivity (Hs) Troponin T
- Assess the effect of BMS-986231 on mortality at Day 182

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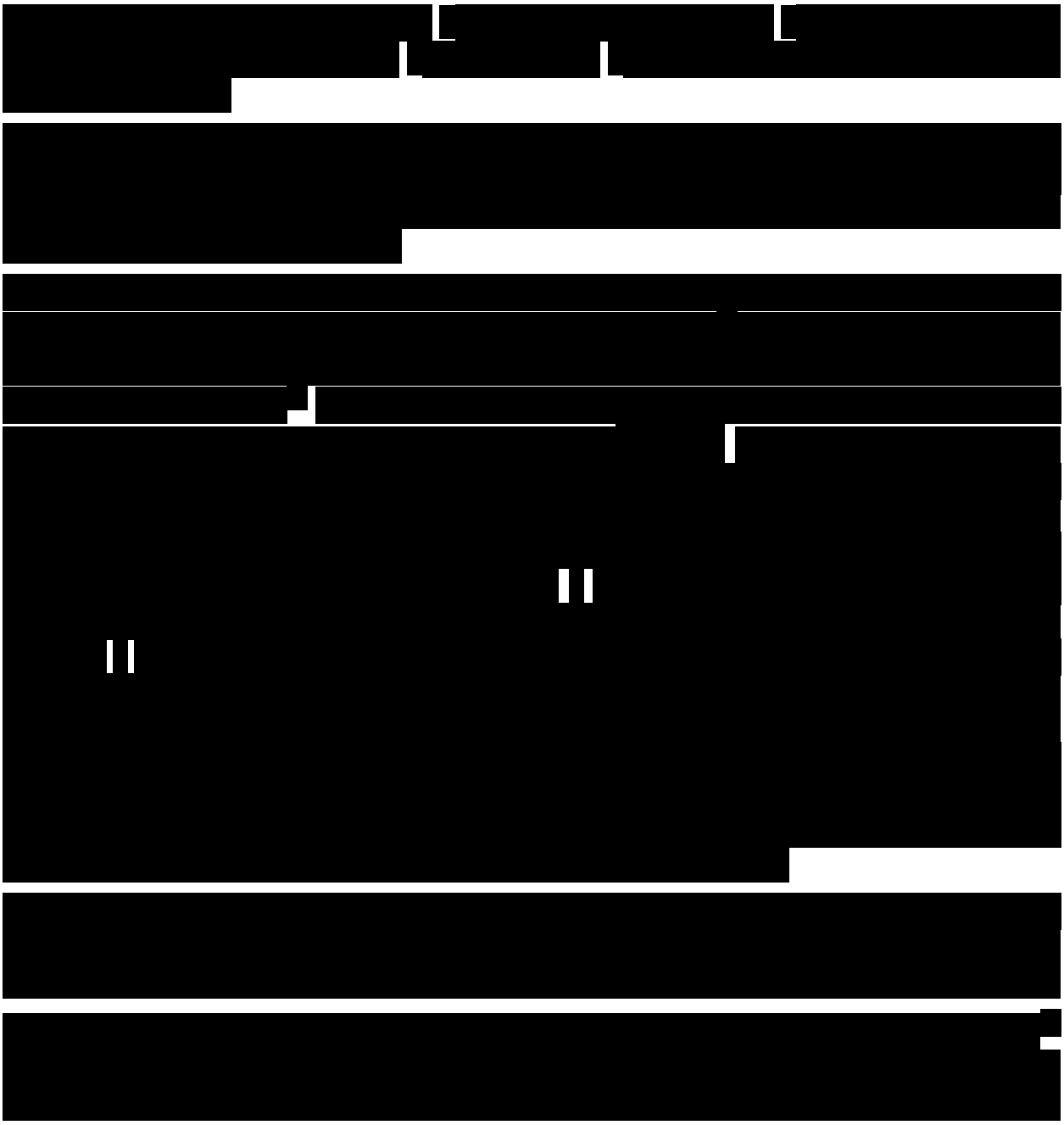


2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

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

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

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

2.2 Institutional Review Board/Independent Ethics Committee

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

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

2.3 Informed Consent

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

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

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 subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study
- Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion

- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information
- If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject
- Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented

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

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a multi-center, randomized, placebo-controlled, double-blind study of continuous 48-hour intravenous (IV) infusions of BMS-986231 in hospitalized HFrEF subjects with ADHF. The trial was designed to identify the doses of BMS-986231 that are safe and tolerated with regard to clinically relevant hypotension.

The study consists of 2 parts, each with a unique cohort of subjects.

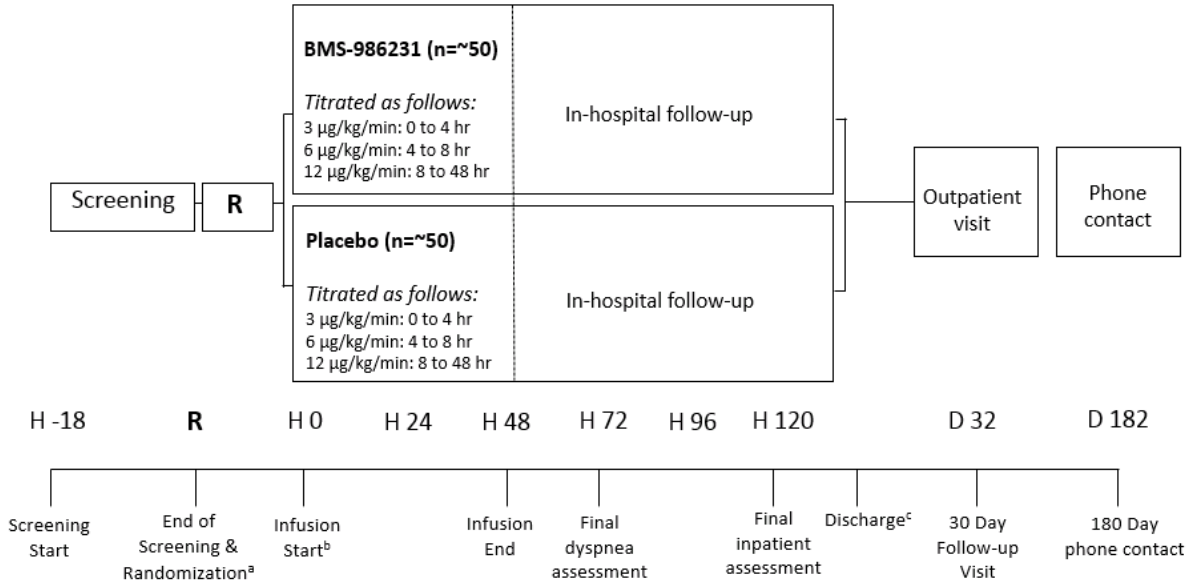
Subjects that are randomized in Part I of the study will not be allowed to participate in Part II.

In Part I (Cohort 1) of the study, approximately 100 subjects will be randomized in a 1:1 ratio to an escalating dose of BMS-986231 (3 μg/kg/min for 4 hours, then 6 μg/kg/min for another 4 hours, then 12 μg/kg/min for the remaining 40 hours) or an escalating dose of placebo.

In Part II (Cohort 2) of the study, the 2 highest planned doses of BMS-986231 in Cohort 1, BMS-986231 6 μg/kg/min and BMS-986231 12 μg/kg/min, will be administered. Approximately 210 subjects will be randomized in a 1:1:1 ratio to one of the 2 active doses of BMS-986231 or placebo. If BMS-986231 12 μg/kg/min is not considered to be a tolerated dose in Part I, then BMS-986231 3 μg/kg/min and BMS-986231 6 μg/kg/min will be evaluated in Part II. In the event that neither 6 μg/kg/min nor 12 μg/kg/min are tolerated, the protocol will require modification.

The study design schematic is presented in Figure 3.1-1 for Part I (Cohort 1) and Figure 3.1-2 for Part II (Cohort 2).

Figure 3.1-1: Study Design Schematic Part I (Cohort 1)

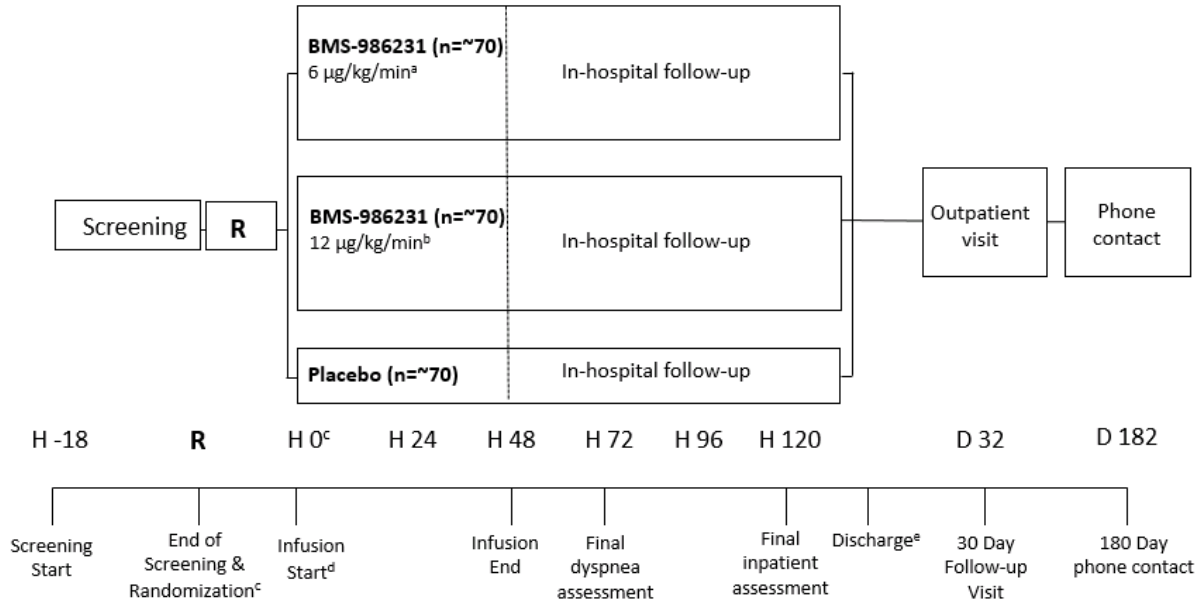


[a] Every effort should be made to initiate study drug administration promptly after randomization

[b] Study Medication infusion must start within 18 hours of presentation (or 48 hours in Part II Cohort 2 of the trial), with presentation defined as the first dose of diuretic for current episode, but not within 2 hours after an IV bolus dose of intravenous diuretics, or within 2 hours after the initiation or an increase in the dose of an IV diuretic administered by continuous infusion

[c] Discharge may occur as per standard medical practice. It is recommended that subjects remain in the hospital for at least 24 hours after the completion of the 48-hour infusion of study drug for safety monitoring

Figure 3.1-2: Study Design Schematic Part II (Cohort 2)



[a] 3 µg/kg/min if 12 µg/kg/min is not tolerated in Part I

[b] 6 µg/kg/min if 12 µg/kg/min is not tolerated in Part I

[c] Every effort should be made to initiate study drug administration promptly after randomization

[d] Study Medication infusion must start within 18 hours of presentation for Part I Cohort 1 (or 48 hours of presentation for Part II Cohort 2), with presentation defined as the first dose of diuretic for current episode, but not within 2 hours after an IV bolus dose of intravenous diuretics, or within 2 hours after the initiation or an increase in the dose of an IV diuretic administered by continuous infusion

[e] Discharge may occur as per standard medical practice. It is recommended that subjects remain in the hospital for at least 24 hours after the completion of the 48-hour infusion of study drug for safety monitoring.

Subjects must be randomized and treated within 18 hours of presentation for Part I Cohort 1 (or 48 hours of presentation for Part II Cohort 2). Presentation is defined as the first dose of IV diuretic for the current episode of ADHF. In addition, subjects must not be randomized within 2 hours following an IV bolus dose of diuretic, or within 2 hours after the initiation or an increase in the dose of an IV diuretic administered by continuous infusion. It is recommended that subjects remain in the hospital for at least 24 hours after the completion of the 48-hour infusion of study drug for safety monitoring.

Every effort must be made to initiate study drug administration promptly after randomization.

The inpatient period will end in conjunction with the final in-patient assessment at Hour 120 or discharge, whichever comes first. All subjects will be followed for safety and rehospitalization endpoints through Day 32 and mortality through Day 182.

The start of the trial is defined as the first subject screened. End of trial is defined as the last subject's final follow-up visit on Day 182, or the last subject's scheduled procedure shown in the Time & Events schedule.

3.2 Post Study Access to Therapy

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

3.3 Study Population

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

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

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

2) Target Population

a) Subjects being hospitalized for ADHF

b) Have had at least 40 mg furosemide intravenous, or equivalent (e.g 40 mg furosemide equivalent to 20 mg torsemide or to 1 mg bumetanide) for the current ADHF episode

c) Subject must be randomized and treated within 18 hours of first dose of intravenous diuretic for Part I Cohort 1 (or 48 hours of first dose for Part II Cohort 2).

d) Have dyspnea at rest or with minimal exertion after administration of at least 1 dose of intravenous diuretics. Subject must not be randomized within 2 hours after an IV bolus dose of intravenous diuretics, or within 2 hours after the initiation or a dose increase of an IV diuretic administered by continuous infusion

e) Have a history of heart failure and a left ventricular ejection fraction (LVEF) ≤ 40%, as assessed by echocardiography, a multigated acquisition (MUGA) scan or magnetic resonance imaging (MRI) scan

Note: Ejection fraction documentation up to 18 months prior to screening may be used if there is no clinical expectation of improvement in ejection fraction in that timeframe (eg, the patient has not had biventricular pacing initiated during that period)

f) Have at least 2 of the following at time of screening:

i) evidence for pulmonary congestion on chest x-ray

ii) rales by chest auscultation,

iii) edema ≥ 2+ on a 0 to 3+ scale (easily identifiable indentation, skin rebounds in 15-30 seconds)

iv) presence of jugular venous distention

g) Have an elevated NT-proBNP ≥ 1600 pg/mL (189 pmol/L) or BNP ≥ 400 pg/mL (116 pmol/L) as determined at the local laboratory within 18 hours prior to the start of study drug infusion for Part I Cohort 1 (or 48 hours for Part II Cohort 2)

For subjects with atrial fibrillation: NT-proBNP ≥ 2400 pg/ml or BNP ≥ 600 pg/ml

h) Body weight ≥ 50 kg and < 140 kg at screening

i) Subject Re-Screening: This study permits the re-screening of a subject that has discontinued the study as a screen failure (has not been randomized). See Section 5.1.1 for more details

3) Age and Reproductive Status

a) Males and Females, at least age 18 (or age of majority) (Germany only, see Appendix 3)

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 18 hours prior to the start of study treatment for Part I Cohort 1 (or 48 hours for Part II Cohort 2)

c) Women must not be breastfeeding

d) WOCBP must agree to follow instruction for methods of contraception for 32 days after discontinuation (duration of study drug plus 30 days duration of one ovulatory cycle)

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for 92 days after discontinuation (duration of study drug plus 90 days (duration of sperm turnover)

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

Investigators shall counsel WOCBP, and male subjects 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 1), 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.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Systolic blood pressure (SBP) < 105 mm Hg or > 160 mm Hg at screening

b) Systolic blood pressure (SBP) < 105 mm Hg or > 160 mm Hg just prior to randomization

c) Heart rate < 50 beats per minute (bpm) or > 130 bpm at screening

d) Heart rate < 50 beats per minute (bpm) or > 130 bpm just prior to randomization

e) Have 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: Functional mitral regurgitation, as well as restrictive mitral inflow pattern on echocardiography is not exclusionary

f) Have a body temperature ≥ 38.5°C (101.3°F) at any time from screening to randomization

g) Have an active infection requiring current IV anti-microbial treatment

2. **Medical History and Concurrent Diseases**
   a) Considered clinically unstable for other conditions than acute heart failure, either because of acute coronary syndrome or ongoing arrhythmia (or be receiving concomitant parenteral therapy with any antiarrhythmic drugs), or other unstable non-cardiovascular disease
   b) Suspected acute lung disease (e.g. pneumonia or asthma) or severe chronic lung disease (e.g. severe chronic obstructive pulmonary disease, pulmonary fibrosis, patients with hypercapnia or requiring home oxygen therapy or chronic oral steroids.)
   c) Have a history of sudden cardiac death with resuscitation within the past 6 months
   d) Be hospitalized with acute coronary syndrome, coronary revascularization or acute myocardial infarction during the previous 90 days prior to screening
   e) 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
   f) Serious comorbid noncardiovascular disease in which the life expectancy of the subject is < 6 months (eg, acute systemic infection – sepsis, metastatic cancer, or other serious illnesses)
   g) Severe 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) (Germany only, see Appendix 3)
   h) Prior cardiac or renal transplant

3. **Physical and Laboratory Test Findings**
   a) Have persistent abnormal serum electrolytes not resolved before randomization, as defined by any of the following:
      i) A sodium (Na+) concentration < 130 or >145 mEq/L (mmol/L)
      ii) A potassium (K+) concentration < 3.2 or >5.5 mEq/L (mmol/L)
   b) Have severe anemia, as documented by a hemoglobin < 9 g/dL (< 5.59 mmol/L) (Germany only, see Appendix 3)
   c) Have severe renal insufficiency before randomization (and during the current hospitalization) defined as an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 [based on any standard limit and equation employed by the local lab, eg, Modification of Diet in Renal Disease (MDRD) equation]. For patients with eGFR values less than but close to 30 mL/min/1.73m^2 upon testing, retesting is allowed.

4. **Prior and Concomitant Medications or Treatments**
   a) Subjects administered IV or transdermal nitrate therapy prior to randomization, except if all 3 of the following criteria are met:
      i) Systolic blood pressure at screening or just prior to randomization is > 120 mm Hg **AND**
      ii) The IV nitroglycerin dose is < 100 µg/min (or isosorbide dinitrate < 3 mg/hour), AND
      iii) The infusion rate and dose has been unchanged for > 2 hours
   b) History of chronic or intermittent renal support therapy (hemodialysis, ultrafiltration, or peritoneal dialysis)
   c) Subjects treated during the current hospitalization with IV vasoactive drugs such as dopamine, dobutamine, enoximone, nesiritide, nitroprusside, levosimendan, amrinone or

milrinone, carperitide or nicorandil prior to start of study drug infusion, or have an anticipated need to be treated with any of these agents during the study drug infusion

d) Subjects treated with oral phosphodiesterase type 5 (PDE5) inhibitor sildenafil, vardenafil or avanafil within 24 hours of screening or treated with tadalafil within 4 days of screening, oral vasopressin V2 receptor antagonist (e.g. tolvaptan) or oral inotropic agents (e.g. pimobendan)

e) Subjects receiving any mechanical ventilation at the time of screening

f) Subjects receiving non-invasive ventilation (CPAP/BiPAP) < 2 hours prior to randomization

5. Allergies and Adverse Drug Reaction

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

6. Other Exclusion Criteria

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

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

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

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

3.3.3 Women of Childbearing Potential

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

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

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

- 8 week minimum for oral products

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

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

- Initiation of PDE5 inhibitors or pimobendan is prohibited during study drug infusion and 24 hours after the end of the study drug
- The use of nitrates, except for subjects receiving stable IV dose of nitrates at randomization, should be avoided, unless clinically indicated (ie, episodes of angina, worsening HF)
- Administration of IV vasoactive drugs (such as dopamine, dobutamine, enoximone, nitroprussiate, levosimendan or milrinone) should be discouraged unless clinically warranted (ie, if patient's status requires use of vasoactive treatments for conditions such as worsening heart failure)

3.4.2 Other Restrictions and Precautions

Not applicable.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

The below discontinuation criteria apply to both Part I (Cohort 1) and Part II (Cohort 2) of the trial.

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

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- If study medication has been interrupted for low blood pressure, resumed, and an episode of hypotension (or symptoms of hypotension) reoccurs (see Section 4.5.1)

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

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

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

3.6 Post Study Drug 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 subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

3.6.1 Withdrawal of Consent

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

3.6.2 Lost to Follow-Up

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

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

lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

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

Treatments:

BMS will provide Investigational drug product BMS-986231 for infusion (active pharmaceutical ingredient BMS-986231 formulated with Captisol® 3405 mg/vial) to all sites as per Table 4-1. In addition, Potassium acetate is to be locally sourced by sites within the US and will be supplied to all ex-US sites as per Table 4-1.

Table 4-1: Study Drugs for CV013011 - Part I (Cohort 1) and Part II (Cohort 2)

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-986231 For Injection	BMS-986231 240 mg/vial	IP	Open Label	White to pale yellow whole or fragmented cake in a 20 mL glass vial with Fluortec™ stopper and a blue flip-off aluminum cap. Secondary packaging is a carton containing 5 or 6 vials.	2 to 8°C (36-46°F) Store in original package, protect from light.
Potassium Acetate Injection, USP[a]	2 mEq/mL (20mL/vial)	Non-IMP	Open Label	Colorless solution in a 20 mL fliptop glass vial. Secondary packaging is a carton containing 6 vials	Store at 20 to 25°C (68 to 77°F).

[a] Supplied by BMS only to ex-US sites

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

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

Study medication will be prepared by an unblinded pharmacist (or appropriate designee) at time of randomization. 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.

4.2 Non-Investigational Product

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

In this study, the required Potassium Acetate used in the active and placebo infusions is considered non-investigational product.

4.3 Storage of Study Drug

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS and listed in Table 4-1 and drug product label. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and BMS contacted immediately.

Please refer to Pharmacy Manual for additional guidance on storage of study drug. Study drug not supplied by BMS will be stored in accordance with the package insert. Please refer to Section 9.2.2 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.

4.4 Method of Assigning Subject Identification

At the time of screening for both Part I (Cohort 1) and Part II (Cohort 2), each subject will be assigned a unique sequential subject number by interactive response technology (IRT). The IRT will be available 24 hours per day, 7 days a week. The subject number will consist of a unique

5 digit number which is assigned sequentially within a study (starting with 00001) by the IRT. This number will be used for identification throughout the study and will not be used for any other subject. Subjects screened for Part I, (Cohort 1) will be assigned sequential study numbers beginning with 00001, and subjects screened for Part II, (Cohort 2) will be assigned sequential study numbers beginning with 10001.

Randomization schedules will be generated by BMS and kept by the IRT vendor. Subjects who meet the inclusion/exclusion criteria will be randomly assigned by the IRT to placebo or an incremental dose of BMS-986231 (3 - 6 - 12 µg/kg/min) in a 1:1 ratio for Part I (Cohort 1) and placebo or 1 of the 2 active dose levels of BMS-986231 in a 1:1:1 ratio for Part II (Cohort 2).

Randomization will be stratified by region.

4.5 Selection and Timing of Dose for Each Subject

Subjects will be administered study medication as a continuous IV infusion over 48 hours.

Body weight measured at screening will be used for dose calculations.

Every effort must be made to initiate study drug administration promptly after randomization.

See Pharmacy Manual for additional dosing information.

4.5.1 Dose Reductions, Temporary Interruptions, and Permanent Discontinuations of Study Drug Due to Blood Pressure

Any decision to lower the dosage level of study drug or discontinue study drug should be based on the Investigators assessment of the subject's overall clinical stability, in the context of appropriate ongoing monitoring of the subject's condition. A 50% dosage adjustment downward maybe be achieved by decreasing the rate of study drug infusion.

In Part I (Cohort 1) subjects who require a dose reduction or temporary interruption during the first infusion period, hours 0 to 4 (dose of 3 µg/kg/min), will be permanently discontinued from study drug.

Study drug infusion rate may be reduced by 50%, temporarily interrupted, or permanently discontinued. See Figure 4.5.1-1 and the following sections for more detail.

Dose Reduction:

- If the subject experiences SBP < 95 mm Hg, without symptoms related to hypotension, the measurement must be repeated within 15 minutes. If the SBP remains < 95 mm Hg, the dose reduction must occur
- A 50% dosage adjustment downward may be achieved by decreasing the rate of study drug infusion by half
- After a dose reduction, the dose cannot be increased again

Temporary interruption:

- If the systolic blood pressure reduces below < 85 mm Hg, and remains < 85 mm Hg during a repeated measure within 15 minutes, the study drug must be interrupted for at least 1 hour
- For subjects that report symptoms consistent with hypotension (eg, dizziness, lightheadedness, etc.), and are related to hypotension, study drug must be interrupted for at least 1 hour

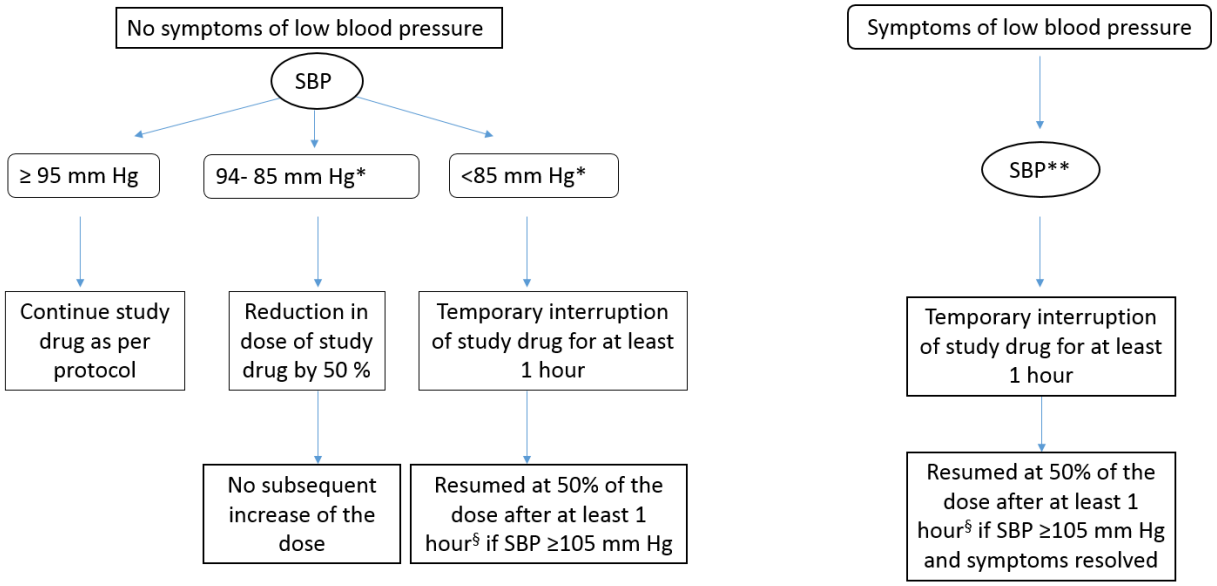
Resuming Study Drug

- Study drug may be resumed at 50% of the dose after 1 hour interruption, if SBP rises to values ≥ 105 mm Hg and any symptoms of hypotension, if present, have resolved.
- If after 4 hours, the subject's SBP remains below < 105 mm Hg, or if symptoms persist, then study drug must be permanently discontinued
- After a dose reduction, the dose cannot be increased again

Permanent discontinuation of the infusion:

- At any time during the administration of study drug, the study drug infusion must be discontinued if an AE or any other safety issue suggests it is not in the subject's best interest to continue to receive study drug
- Study drug will be permanently discontinued after it has been down titrated once, and criteria for dose reduction or interruption has been met again.

Figure 4.5.1-1: Guidance for Dose Reduction Based on Blood Pressure Measurements and/or Symptoms of low blood pressure



* Confirmed by a second measure within 15 min

** No need to wait for confirmatory measures within 15 min

§ But no more than 4 hours

4.6 Blinding/Unblinding

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

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

For this study, the method of unblinding for emergency purposes is 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 subject for non-emergency purposes should be discussed with the Medical Monitor.

4.6.2 Other Blinding and Unblinding

The Data Monitoring Committee (DMC; see Section 7) will assess safety on an ongoing basis, and will have access to unblinded treatment codes for individual subjects. An analysis team, including a reporting statistician and programming support, who are not involved with the conduct of the study, will provide analyses to the DMC.

Two interim analyses will be performed in this study.

The first unblinded interim analysis will be performed by the analysis team at the completion of the last visit at Hour 120 in Part I (Cohort 1). This analysis will be reviewed by the DMC and will be reviewed in parallel and by the executive committee (see Section 7) and Sponsor representatives. The rationale for a fully unblinded review by the executive committee and Sponsor is to determine whether 12 μg/kg/min is an appropriate dose to study in Part II.

The second interim analysis will be performed following completion of the last visit at Day 32 in Part II (Cohort 2). The study analysis team will then provide top-line results to the project team.

The follow-up to Day 182 for both Part I and Part II will be site-and-subject blinded.

The Bioanalytical Sciences section or its designate may be unblinded to the randomized treatment assignments in order to minimize unnecessary assays of samples from control group subjects. Likewise, the Biotransformation section or its designate may be unblinded, if metabolite profiling work is conducted.

In certain circumstances a pharmacokineticist or designates in Clinical Pharmacology and Pharmacometrics, biostatisticians and programmers 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 assignments.

The pharmacist at the site and/or its designate will be unblinded to the randomized treatment assignments in order to dispense treatment from bulk supplies, as needed. An unblinded Site Monitor, not involved with other study conduct, will be assigned exclusively to reconcile study medication and assure accountability.

Except as noted above, other members of BMS Research and Development personnel, as well as all vendors responsible for the conduct of the trial (protocol team) will remain blinded.

4.7 Treatment Compliance

Not applicable.

4.8 Destruction or Return of Investigational Product

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

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

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

- On-site disposal practices must not expose humans to risks from the drug
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances

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

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

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

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

4.9 Retained Samples for Bioavailability / Bioequivalence

Not Applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (CV013011)

Procedure	Screening Visit (-18 for Part I Cohort 1 or -48 for Part II Cohort 2, up to 0 hours)	Pre-Randomization Procedures	Notes
Eligibility Assessments			
Informed Consent	X		
Review Inclusion/Exclusion Criteria	X	X	
Medical History	X		
Confirm administration of IV diuretic and time of administration	X		
Safety Assessments			
Complete Physical Examination	X		
Body Weight	X		
Height	X		
Vital Signs: Blood Pressure and Heart Rate	X	X*	Perform Semi-Recumbent (at a 30º angle). *Within 15 minutes prior to randomization
Respiratory Rate	X	X	
Use of Oxygen Supplementation, Oxygen Saturation	X	X	
Temperature	X	X*	*Within 15 minutes prior to randomization
Chest X-ray	X		As applicable, refer to section 3.3.1 X-ray obtained for the current episode of ADHF as part of standard of care may be used.

Table 5.1-1: Screening Procedural Outline (CV013011)

Procedure	Screening Visit (-18 for Part I Cohort 1 or -48 for Part II Cohort 2, up to 0 hours)	Pre-Randomization Procedures	Notes
12-Lead ECG (Electrocardiogram)	X		
Telemetry Monitoring		X	Begin within 2 hours prior to start of study medication infusion
Holter Monitoring (Part II Cohort 2 Only)		X	For participating sites. Begin within 2 hours prior to start of study medication infusion
Investigator Assessment of Congestion		X	Physical exam to assess signs and symptoms of congestion will include symptom assessments (dyspnea on exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea, persistent coughing or wheezing, fatigue, and abdominal discomfort), and signs assessment (peripheral edema, pulmonary rales, tachypnea and/or oxygen desaturation, increased jugular venous pressure, hepatomegaly, ascites).
Serious Adverse Events Assessment	X	X	Begins at time subject signs ICF
Review concomitant medications/procedures	X	X	
Local Laboratory Assessments			See Section 5.3.5.1 for Analytes
Hematology and Serum Chemistry	X		
eGFR	X		
Trough Serum Digoxin	X		If receiving digitalis glycosides
Hs Troponin T	X		
Coagulation Tests	X		Prothrombin Time (PT or PT-INR)
NT-proBNP or BNP	X		As per site preference

Table 5.1-1: Screening Procedural Outline (CV013011)

Procedure	Screening Visit (-18 for Part I Cohort 1 or -48 for Part II Cohort 2, up to 0 hours)	Pre-Randomization Procedures	Notes
Pregnancy Test	X		
Central Laboratory Assessments			See Section 5.3.5.2 for Analytes
Hematology and Serum Chemistry		X	
Hs Troponin T		X	
NT-proBNP, Serum Cystatin C, NGAL		X	
CRP		X	
Urinalysis		X	
Urine creatinine, Na+, and K+		X	
[redacted]			
Efficacy Assessments			
Resting Dyspnea measured by the Numerical Rating Scale (NRS)[a]		X	
Other Assessments			
Sensory Motor Survey		X	

[a] If subject is receiving supplemental oxygen, perform NRS without removing oxygen

Table 5.1-2: Treatment and In-Hospital Follow-up (CV013011)

Procedure	Hour 0-23[a] (Post Rand, Day 1)	Hour 24 ± 2	Hour 48 ± 2	Hour 72 ± 2	Hour 96 ± 2	Hour 120 ± 2 or Discharge [b c]	Notes (Time is relative to start of dosing)
Randomize Subject	X						Randomization must take place before Hour 0
Administer Study Medication	X						48 hour continuous infusion ***Study medication infusion begin promptly after randomization***
Safety Assessments							
Body Weight		X	X	X	X	X	
Vital Signs: Blood Pressure and Heart Rate[d]	X	X	X	X	X	X	Perform Semi-Recumbent (at a 30º angle) Day 1: Hours 0, 0.5, 1, 2, 4, **5***, 6, 8, **9***, 10, 12, 14, 16, 18, 20, 22 Hours: 24, 28, 32, 36, 40, 44 Hours 48, 54, 60, 66 Hour 72 Hour 96 Hour 120 Perform measurements before IV bag change, when possible. Repeats as per Section 5.3.1 Perform also if signs or symptoms of hypotension *Part I (Cohort 1) only
Respiratory Rate	X	X	X	X	X	X	Day 1: Hours 6 and 12
Use of Oxygen Supplementation, Oxygen Saturation	X	X	X	X	X	X	Day 1: Hours 6 and 12

Table 5.1-2: Treatment and In-Hospital Follow-up (CV013011)

Procedure	Hour 0-23[a] (Post Rand, Day 1)	Hour 24 ± 2	Hour 48 ± 2	Hour 72 ± 2	Hour 96 ± 2	Hour 120 ± 2 or Discharge [b c]	Notes (Time is relative to start of dosing)
Temperature		X	X	X	X	X	
12-Lead ECG		X	X	X		X	
Telemetry Monitoring	X						Continuous monitoring through Hour 50
Holter Monitoring (Part II Cohort 2 Only)	X						For participating sites. Continuous monitoring through Hour 52. 12-lead ECGs will be extracted at 3 timepoints prior to the start of the infusion and at the same timepoints as PK determinations up to and including 48 hours post-dose (See section 5.5) Subjects will be supinely resting in a semi-recumbent position for at least 10 minutes prior to and 5 minutes after each timepoint for ECG extraction (Day 1: Hour 0.75, 4*, 8*, 14, 48 and Hour 52). When ECG extractions coincide with 12-lead safety ECGs, blood draws and other assessments, ECG extractions should, when feasible, be performed in said order.
Investigator Assessment of Signs of Congestion		X	X	X	X	X	Physical exam to assess signs and symptoms of congestion will include symptom assessments (dyspnea on exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea, persistent coughing or wheezing, fatigue, and abdominal discomfort), and

Table 5.1-2: Treatment and In-Hospital Follow-up (CV013011)

Procedure	Hour 0-23[a] (Post Rand, Day 1)	Hour 24 ± 2	Hour 48 ± 2	Hour 72 ± 2	Hour 96 ± 2	Hour 120 ± 2 or Discharge [b c]	Notes (Time is relative to start of dosing)
							signs assessment (peripheral edema, pulmonary rales, tachypnea and/or oxygen desaturation, increased jugular venous pressure, hepatomegaly, ascites).
Assessment of Hypotension	X		X	X			Assessment of signs and symptoms of hypotension.
Serious Adverse Event Assessment	X						
Adverse Events Assessment	X						From Hour 0 to Hour 120. If subject is discharged before Hour 120, site asked to contact subject at Hour 120 for final AE collection
Concomitant Medications	X						
Local Laboratory Assessments							
Cumulative Urinary Output (Volume)		X	X	X	X	X	Provide daily volume
Pregnancy Test				X		X	WOCBP only
Central Laboratory Assessments							See Section 5.3.5.2 for Analytes
Hematology and Serum Chemistry		X	X	X		X	
Hs Troponin T		X	X	X		X	
NT-proBNP, Serum Cystatin C, NGAL		X	X	X		X	
CRP			X			X	
Urinalysis				X			

Table 5.1-2: Treatment and In-Hospital Follow-up (CV013011)

Procedure	Hour 0-23[a] (Post Rand, Day 1)	Hour 24 ± 2	Hour 48 ± 2	Hour 72 ± 2	Hour 96 ± 2	Hour 120 ± 2 or Discharge [b c]	Notes (Time is relative to start of dosing)
Urine creatinine, Na+ and K+		X	X	X		X	
Pharmacokinetics							See Section 5.5
Pharmacokinetic Blood Samples Collection and Preparation of Blood Samples	X		X	X			Part I Cohort 1: Day 1: Hour 0.75, 4, 8, 14 Hour 48 Hour 52 Part II Cohort 2: Day 1: Hour 0.75, 6, 14 Hour 48 Hour 52 Perform measurements before IV bag change or stopping the infusion, whenever possible. Collect sample when dose lowered due to a safety event and also at time of early discontinuation of study drug.
[redacted]							

Table 5.1-2: Treatment and In-Hospital Follow-up (CV013011)

Procedure	Hour 0-23[a] (Post Rand, Day 1)	Hour 24 ± 2	Hour 48 ± 2	Hour 72 ± 2	Hour 96 ± 2	Hour 120 ± 2 or Discharge [b c]	Notes (Time is relative to start of dosing)
Efficacy Assessments							
Resting Dyspnea measured by Numerical Rating Scale (NRS)[e]	X	X	X	X		X	Day 1: Hours 6 and 12
Resting Dyspnea measured by 7-point Likert Scale[e]	X	X	X	X		X	Day 1: Hours 6 and 12
Patient Global Assessment measured by 7-point Likert Scale[e]	X	X	X	X		X	Day 1: Hours 6 and 12
Assessments of Worsening Heart Failure		X	X	X	X	X	Documentation of Worsening Physical Signs and Symptoms of Heart Failure, and Documentation of Initiation or Increased dose of Parenteral Diuretic, Vasodilator and/or Inotropes, or Need for Mechanical interventions (mechanical ventilation, circulatory support, ultrafiltration or dialysis). Assessments to cover prior 24 hour period.
Wristworn Actigraphy monitoring device (watch) (Part II Cohort 2)			X	X	X	X	For participating sites. Provide the device to subjects at the end of the 48 hours infusion or when the study drug has been permanently discontinued
Other Assessments							
Sensory Motor Survey						X	

[a] Hour 0 defined as start of study medication infusion

[b] Visit to occur at Hour 120 ± 2 or Discharge, whichever comes first. If subject is discharged after Hour 120, no further protocol in-hospital visits are completed

[c] Assessments required at Discharge Visit should not be repeated if performed within previous 12 hours

[d] Vital signs should be taken within (± 0.25)

[e] If subject is receiving supplemental oxygen, perform NRS without removing oxygen

Table 5.1-3: Outpatient Follow-up (CV013011)

Procedure	Day 32 (± 2 Days) Clinic Visit	Day 182 (± 5 Days) Phone Visit	Notes
Safety Assessments			
Vital Signs: Blood Pressure and Heart Rate	X		When possible, perform Semi-Recumbent (at a 30º angle)
Respiratory Rate	X		
Body Weight	X		
Temperature	X		
Serious Adverse Events Assessment	X		
Local Laboratory Assessments			
Pregnancy Test	X		WOCBP only
Central Laboratory Assessments			See Section 5.3.5.2 for Analytes
Hematology and Serum Chemistry	X		
NT-proBNP, Serum Cystatin C, NGAL	X		
CRP	X		
Urinalysis	X		
Urine creatinine, Na+ and K+	X		
[redacted]			
Efficacy, Safety, and Other Assessments			
Healthcare Utilization Assessment	X		
Assessment of Mortality	X	X	
Sensory Motor Survey	X		

Table 5.1-3: Outpatient Follow-up (CV013011)

Procedure	Day 32 (± 2 Days) Clinic Visit	Day 182 (± 5 Days) Phone Visit	Notes
Actigraphy monitoring watch (Part II Cohort 2)	X		For participating sites. One time complete transfer of data from the actigraphy device to a dedicated website via an electronic docking station to occur during or immediately following the 32-days study visit

5.1.1 Retesting During Screening or Lead-in Period

All screening laboratory will be performed locally, and tests may be repeated at the discretion of the Investigator as per site policy.

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

In an effort to find all possible well-qualified subjects, subjects that have discontinued the study as a screen failure (have not been randomized) are eligible for re-screening upon presentation for a subsequent episode of ADHF at the discretion of the Investigator.

If re-screened, the subject must be re-consented and a new subject number will be assigned by the IRT. Laboratory parameters and/or assessments that are included in Table 5.1-1, Screening Procedural Outline, must be repeated. The subject numbers and data will be linked in the clinical database.

5.1.2 Discharge

Discharge may occur as per institutions standard medical practice. It is recommended that subjects remain in the hospital for at least 24 hours after the completion of the 48-hour infusion of study drug for safety monitoring.

Subjects discharged prior to Hour 120 should complete the Hour 120/Discharge visit. Assessments required at the Hour 120/Discharge Visit as per Table 5.1-1 should not be repeated if performed within the previous 12 hours.

5.2 Study Materials

- 11-item Numerical Rating Scale
- 7-point to Likert Scale
- Sensory Motor Survey
- Pharmacy Manual
- Clinical Laboratory Manual
- Subject education materials and other site support tools

5.3 Safety Assessments

Additional procedures and assessments may be performed as a part of the subject's standard of care; however, data for these assessments will remain in the subject's medical record and is not be provided to BMS, unless needed to support an AE, SAE report, or as specifically requested by the Sponsor.

5.3.1 Assessment of Blood Pressure and Symptoms for Hypotension

The primary endpoint of the study is the incidence of clinically relevant hypotension, defined by SBP < 90 mm Hg (confirmed by a repeated value < 90 mm Hg) or symptoms of hypotension, up to 6 hours after the end of study drug infusion. Thus hypotension will be assessed by collection of symptoms and blood pressure measurements.

Symptomatic hypotension is defined as the presence of both low SBP and significant and/or non-resolving symptoms due to low blood pressure (eg, lightheadedness, dizziness, etc.).

Blood pressure measurements should be performed with the subject in a semi-recumbent (about a 30º angle) position, whenever possible.

Blood pressure will be measured as indicated in Table 5.1-2, within (± 0.25) of the specified time points. In addition, sites may perform measurements at intervals defined by institutional standard of care for subjects receiving vasodilators, but no less than what is described in Table 5.1-2.

If the study drug dose is modified (decreased, interrupted, resumed or discontinued) the frequency of blood pressure measurements will follow a more intensive schedule for up to 6 hours following the dose modification (Table 5.3.1-1). Upon completion of the intensive schedule, measurements can be either resumed per the original schedule, or follow the discontinuation schedule if the drug is permanently discontinued.

Table 5.3.1-1: Schedule of Intensive Blood Pressure Collection Following a Dose Modification

	30 minutes post	1 hour post	2 hours Post	4 hours post	6 hours post
Dose reduction	X	X	X	X	X
Dose interruption[a]	X	X	X	X	
Dose resumption[b]	X	X	X	X	X
Dose discontinuation	X	X	X	X	X[c]

[a] dose must be resumed within 4 hours of dose interruption. If interruption last beyond 4 hours, dose must be discontinued and discontinuation schedule must be followed.

[b] If dose is restarted within 4 hours following interruption, follow schedule for dose resumption

[c] After 6 hours, continue collecting blood pressure measurement at a minimum of every 12 hours through hour 72 or follow the local institutional standard of care protocol, whichever is more frequent.

In addition to assessments of blood pressure, the Investigator will be asked to collect and assess signs and symptoms of low blood pressure The details to be captured will include:

- Onset date/time
- Total duration of episode
- Lowest blood pressure during the episode
- Signs and symptoms associated with low blood pressure (such as confusion, dizziness, fatigue, auditory disturbances (such as tinnitus), lightheadedness, chest pain, visual disturbances, vomiting, syncope, etc)

Events of clinically relevant hypotension will also be recorded as an Adverse Event (see Section 6) Management of study drug (interruption, discontinuation, re-start) is detailed in Section 4.5.1. Hypotension endpoints are defined in Section 8.3.

5.3.2 Physical Measurements

Height: Measurement of height should be performed with the subject's shoes removed, if possible. The subject's knees should be straightened, head held erect, and eyes forward.

Weight: Measurement of weight should be performed with the subject having pockets empty, shoes removed, and bladder empty, when possible.

5.3.3 Physical Examination

A complete physical examination should include general appearance, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdomen, lymph nodes, extremities, neurological, skin, and musculoskeletal.

The individual performing the physical examinations must be licensed by state law (or applicable local law) to perform a physical examination.

5.3.4 Electrocardiogram

The Investigator should review and assess all ECGs for any clinically significant abnormalities, and initial and date the report.

The site should follow their standard practices for performing ECGs. Below is guidance to be used as a reference, if needed:

In preparation for the ECG, ensure there is minimal interference between the skin surface and the electrode. Use alcohol to prepare the skin at each electrode site. Thick chest hair should be shaved to ensure sufficient contact.

Before attaching electrodes to pick-up points, spread the electrode with electrode gel. Place the electrodes on bony areas, avoiding large muscle masses, to achieve better tracings as described below. The subject must be supine and should refrain from movement during the ECG recording.

Ensure that the subject and the electrodes (including the neutral electrode) are not exposed to conducting objects, even if grounded.

- RL: On the right leg (inside calf, midway between knee and ankle)
- LL: On the left leg (inside calf, midway between knee and ankle)
- RA: Right arm (on the inside)
- LA: Left arm (on the inside)
- V1: 4th intercostal space, at right sternal margin
- V2: 4th intercostal space, at left sternal margin
- V3: Midway between V2 and V4
- V4: 5th intercostal space at left midclavicular line
- V5: Same transverse level at V4, at anterior axillary line
- V6: Same transverse level at V4, at left midaxillary line

Keep one original ECG (print-out or electronic copy) in the medical chart and ensure a copy, assessed, initialed and dated by the Investigator, is maintained in the source documents for the study.

5.3.5 Laboratory Test Assessments

Subjects will have laboratory tests performed locally as necessary for treatment of ADHF following local practices. In addition, laboratory tests will be performed locally and centrally as described in the following sections.

5.3.5.1 Local Laboratory Assessments for Screening

The following local laboratory tests will be assessed as part of the screening evaluation. Local Laboratory results obtained for the current episode of heart failure as part of standard of care may be used. 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)
- Alkaline Phosphatase
- Total Bilirubin
- Blood Urea Nitrogen (BUN)
- Electrolytes
  - Sodium
  - Potassium
- Serum Creatinine (Scr)

Other Assessments

- eGFR, by locally used equation
- Trough Serum Digoxin (if receiving digitalis glycosides)
- Hs Troponin T (or other based on site's available assays)
- Coagulation Tests
  - Prothrombin Time (PT or PT-INR)
- NT-ProBNP or BNP (as per site preference)

5.3.5.2 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 in Section 5.

Hematology

- Hemoglobin
- Hematocrit
- White blood cell count and differential
- Erythrocytes (RBC)
- Erythrocyte mean corpuscular volume (MCV)*
- Erythrocyte mean corpuscular hemoglobin (MCH)*
- Erythrocyte mean corpuscular hemoglobin concentration (MCHC)*
- Platelet count
- Reticulocyte count*

  *performed at baseline, Hour 120 or Discharge, whichever comes first, and Day 32

Serum chemistry

- Aspartate Aminotransferase (AST, SGOT)
- Alanine Aminotransferase (ALT, SGPT)
- Alkaline Phosphatase
- Creatine Kinase (Creatine Phosphokinase) (CK) (CPK)
- Total Bilirubin
- Uric Acid
- Blood Urea Nitrogen (BUN)
- Electrolytes
  - Sodium
  - Potassium
  - Chloride
  - Bicarbonate
  - Glucose
  - Anion gap
  - Magnesium
- Total Protein
- Albumin
- Serum Creatinine (Scr)
- Calcium*
- Phosphorus*

  *performed at baseline, Hour 24, Hour 48 and Hour 120 or Discharge, whichever comes first.

Other Assessments

- eGFR, by MDRD
- Trough Serum Digoxin (if receiving digitalis glycosides)
- Hs Troponin T
- Coagulation Tests
  - Prothrombin Time (PT and PT-INR)
  - Partial thromboplastin time (PTT)

- NT-ProBNP
- Cystatin C
- CRP
- NGAL

Urinalysis

- pH, protein, glucose, leukocyte esterase, blood by dipstick
- Microalbumin
- Albumin: creatinine ratio
- Microscopy if dipstick positive for blood, leukocyte esterase or protein

The Central Laboratory and designated reference laboratories for this study will perform the analysis of all scheduled laboratory tests and will provide reference ranges for these tests. Urine dipstick testing for pregnancy (in WOCBP) at specified visits is to be done at the investigative site.

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.

5.3.6 Telemetry Monitoring

Telemetry monitoring will be performed to help monitor subject safety. The site will follow their normal operating procedures established for telemetry monitoring. Clinically significant findings from the telemetry monitoring will be recorded as AEs and SAEs per the Investigators decision.

5.3.7 Holter Recordings

Holter monitoring with extraction of serial ECGs will be performed in a sub-set of 51 patients in Part II Cohort 2 only, randomized 1:1:1 to placebo and the two active doses in Part II Cohort 2 of the study. The 12-lead Holter and ECG equipment will be supplied and supported by the sponsor and a core electrocardiographic laboratory. ECGs to be used in the analyses will be selected by pre-determined time points as defined in the Table of Assessments, and will be read centrally by a core electrocardiographic laboratory. The analysis will be described in detail in a separate analysis plan.

Ten 14-second digital 12-lead ECG tracings will be extracted from the continuous Holter recordings using the 'TQT Plus method', a computer-assisted and statistical process utilized by a core electrocardiographic laboratory.

At each protocol-specified timepoint, 10 ECG replicates will be extracted from a 5-minute "ECG window" (typically, the last 5 minutes of the 15-minute period when the subject is maintained in a supine or semi-recumbent quiet position. Subjects must be instructed to rest in a quiet position 15 minutes before each PK draw.

5.3.8 Imaging Assessment for the Study

Not Applicable.

5.4 Efficacy Assessments

5.4.1 Assessments of Worsening Heart Failure

The Investigator will be asked to indicate if a subject has experienced worsening heart failure, to document the signs, and symptoms that led to the assessment of worsening heart failure, and to document the intensification of treatment implemented for worsening heart failure. Assessment is to be done once daily covering the prior 24-hour period as per the scheduled times in Table 5.1-2.

In this trial, worsening heart failure is defined as **new or worsening signs and/or symptoms of heart failure that require**:

- **Intensification of IV therapy** for heart failure (such as initiation, restart or up-titration of IV diuretics, IV nitrates or other IV vasoactive drugs), *and/or*
- Addition of a mechanical support, either:
  - Ventilatory (mechanical ventilation, noninvasive ventilation),
  - Circulatory (Intra-Aortic Balloon Pump (IABP), ventricular assist device) or
  - Use of ultrafiltration, hemofiltration or hemodialysis specifically for the management of WHF

The presence of WHF must be documented by the investigator recording the signs, symptoms, and/or laboratory assessments that led the conclusion that the subject had worsened.

Symptoms of heart failure may include: dyspnea on exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea, persistent coughing or wheezing, fatigue, and abdominal discomfort.

Signs of heart failure might include: pulmonary rales, tachypnea and/or oxygen desaturation, increased jugular venous pressure, hepatomegaly, peripheral edema, an increase in body weight, oliguria, and signs of hypo-perfusion such as mental confusion, hypotension, and cool skin

5.4.2 Investigator Assessment of Signs of Congestion

The Investigator will be asked to assess the subject's signs of congestion using the following criteria:

1) Bilateral peripheral edema using a 4-point scale
   a) 0 absent
   b) 1+ Trace (Barely perceptible indent, skin rebounds quickly)
   c) 2+ Feet and ankles (Easily identifiable indent, skin rebounds in 15-30 sec, edema limited to feet and ankles)
   d) 3+ Lower legs or thighs (Easily identifiable indent, skin rebounds in > 30 sec, edema extended to lower legs or thighs)
2) Bilateral pulmonary rales: Auscultation of the lungs applying a 3-point scale
   a) 0 absent
   b) 1+ < 1/3 up lung fields,
   c) 2+ ≥ 1/3 up lung fields

3) Jugular venous distension (absent / present)
4) Hepatic enlargement (absent / present)
5) Orthopnea: The subject should be observed after being in the lowest recumbent position for 10-15 minutes
   a) Absent – subject has no sensation of dyspnea in recumbent position
   b) Present - dyspnea develops in the recumbent position and is relieved by elevation of the head with pillows
6) Ascites
   a) Absent
   b) Present

5.4.3 Physical activity monitoring using a wrist-worn actigraphy device (watch)

Physical activity will be measured in a subset of approximately 100 patients in Part II of the trial only, using an actigraphy wearable device worn on the wrist (wristwatch) that utilizes an accelerometer to monitor the occurrence and degree of motion[47].
All sites participating in the accelerometry sub-study will provide the device to subjects at the end of the 48 hours infusion or when the study drug has been permanently discontinued. Study participants accepting to participate in the sub-study will wear the device continuously during 30 days follow-up period, with the exception of the charging period (battery life expected to be approximately 10-12 days), via a charger provided to the patient. Data collected by the device will be uploaded during the 32-days study visit via an electronic docking station at the site.

5.5 Pharmacokinetic Assessments

Blood samples will be collected for pharmacokinetic assessments as described in Table 5.5-1.

Table 5.5-1: Pharmacokinetic Assessments

Time Relative to Dosing Hour (window)	Time (Relative to Dosing) Hour: Min	PK Blood Sample
0.75 (± 0.25)	00:45	X
4 (± 0.5)	04:00	X
8 (± 0.5)	8:00	X
14 (± 4)	14:00	X
48 (± 1)	48:00	X
52 (± 1)	52:00	X
Dose lowered due to safety event (± 0.5)	Misc.	X
Early Discontinuation	Misc.	X

Collect the 4 and 8 hour PK samples immediately prior to the IV bag change whenever possible. In addition, collect a PK sample from the subject 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.

[redacted]

[redacted]

[redacted]

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

5.7 Outcomes Research Assessments

5.7.1 Dyspnea Assessments

The sensation of dyspnea is subjective, but dyspnea relief is important to subjects and has been long quantified in clinical trials using patient-reported outcome scales that have previously been used to assess the efficacy of other interventions in ADHF subjects.

In this trial, subjects are asked to report their absolute current severity of dyspnea on an 11-point numerical rating scale (NRS; range 0 to 10) and their current level of dyspnea relative to baseline using 7-level Likert scales.

5.7.1.1 Dyspnea Numerical Rating Scale

The numerical rating scale (NRS) will be used to assess the degree of dyspnea (breathlessness), measured using an 11-point scale provided by the Sponsor.

5.7.1.2 Dyspnea Likert Scale

Subject will be presented with the following question: "We would like to measure how you think your breathing is. Please circle the number next to the description that best indicates how you are breathing right now, compared to when you first started the study drug."

3 = Markedly better

2 = Moderately better

1 = Minimally better

0 = No change

-1 = Minimally worse

-2 = Moderately worse

-3 = Markedly worse

5.7.2 Healthcare Utilization

Following discharge from the index hospitalization, the occurrence of rehospitalizations and emergency department visits for heart failure and other causes of cardiovascular disease will be documented. Rehosptalizations will include subjects who are either under observation or admitted as an inpatient with a length of stay ≥ 24 hours. Emergency department visits will include urgent, unplanned visits in a monitored healthcare setting with a length of stay < 24 hours. Only emergency department visits that do not result in a hospitalization will be counted as separate healthcare encounters.

In the event that the subject reports rehospitalizations or emergency department visits through Day 32 after the index hospitalization, the reason for the rehospitalization/ED visit will be recorded and, where possible, will be confirmed with the hospital or the subject's physician. The investigator should make every effort to obtain a discharge summary. If the subject is currently hospitalized and unable to attend the visit, then the investigator should make every effort to

reschedule the visit when medically appropriate and to obtain the discharge summary when available.

The primary reason for the rehospitalization/ED visit will be categorized by the investigator into 1 of the following categories:

- Heart failure related event involves a primary diagnosis of HF, where the subject has new or worsening symptoms, objective evidence of new or worsening HF, and receives new or intensification of treatment including an IV diuretic
- Other cardiovascular, non-heart failure related event involves a primary diagnosis of cardiovascular disease other than HF including MI, resuscitate sudden cardiac death or other cardiovascular cause (eg, stroke)
- Non-cardiovascular event involves primary diagnoses other than HF and CV disease

5.7.3 Mortality

Investigators will follow all subjects to Day 182 for mortality.

Investigators will be asked to report deaths and categorize them as either cardiovascular or non-cardiovascular death. All deaths will be assumed to be cardiovascular unless a non-cardiovascular cause can be clearly provided. Below is guidance for Investigator classification:

Cardiovascular Death:

Cardiovascular death includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes

Non-cardiovascular Death:

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

5.8 Other Assessments

5.8.1 Sensory Motor Survey

Subject will be complete a 5 question interview relating to presence and degree of specified characteristics relating to sensory and motor function, with responses indicating either none, mild, moderate, or severe felt over the past 24 hours.

5.9 Additional Research Collection

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

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

This collection for additional research is intended to expand the translational R&D capability at Bristol-Myers Squibb, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority

requests for analysis, and the advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

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

- Residual plasma and serum samples from exploratory biomarker collections (see Table 5.6-1 and Table 5.9-1) will be retained for additional research purposes
- Samples will be securely stored by the BMS Biorepository in Hopewell, NJ or at a BMS approved third party storage management facility
- Samples will be stored in a coded fashion; and no researcher will have access to the key, which is securely held at the clinical site, so that there is no direct ability for a researcher to connect a sample to a specific individual
- Additional research samples will be retained for 15 years or the maximum allowed by applicable law. No additional sampling is required for residual collections

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

Table 5.9-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Time points for which residual samples will be retained
Plasma exploratory biomarker	All
Serum exploratory biomarker	All
Urine	All

6 ADVERSE EVENTS

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

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

Related: There is a reasonable causal relationship between study drug administration and the AE.

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

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

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

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

6.1 Serious Adverse Events

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

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

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

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

Worsening heart failure, including hospital readmission is considered an SAE and should be reported as such.

NOTE:

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

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure

- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing.

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

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

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

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

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

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

All SAEs must be followed to resolution or stabilization.

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

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug and continue through Hour 120.

AEs will be collected from Hour 0 to Hour 120. If a subject is discharged prior to Hour 120, the site is asked to follow-up with the subject at Hour 120 to complete AE collection.

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

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

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE eCRF 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 subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy

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

6.4 Pregnancy

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

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

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

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

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

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

6.5 Overdose

Include any project specific definition of overdose in addition to the following mandatory statement as the last sentence:

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. All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details).

6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

AND No other immediately apparent possible causes of aminotransaminases (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

Given the short treatment course, baseline liver enzyme testing will be performed at Pre-randomization and post-treatment liver enzyme testing will be performed at Hour 120 and Day 32.

All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

7.1 Data Monitoring Committee

An independent DMC will review safety data to ensure subjects safety. The full role of the DMC will be defined in the DMC charter. The DMC will review unblinded accumulating data on a regular basis and make recommendations to BMS and the Executive Committee regarding subjects currently enrolled and yet to be enrolled in the trial. The DMC may recommend suspension of enrolment or early termination of the trial, for safety reasons. See Section 8.5 for additional information.

The DMC will consider available endpoint information, in addition to safety events, before making any study stopping recommendations to the Executive Committee and Sponsor, as per guidelines set forth in the DMC charter.

7.2 Executive Committee

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 interim and final analyses with Sponsor.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

For Part I (Cohort 1), approximately 50 subjects per group will be randomized to placebo or an incremental dose of BMS-986231 (3 - 6 - 12 μg/kg/min). Under a sample decision rule (eg, observed doubling with more than a 4% difference) and assuming clinically relevant hypotension incidences of 5% or 10% in the placebo group, the posterior probabilities of detecting an increase of 4-fold or 3-fold in incidence, respectively, are 86% and 80%, respectively. If there is no increase in clinically relevant hypotension, then the posterior probabilities of falsely detecting an increase are 11-12%.

For Part II (Cohort 2), approximately 70 subjects per group will be randomized to placebo or one of the two active dose levels of BMS-986231. Under a sample decision rule (eg, observed 1.8-fold increase with more than a 3% difference) and assuming clinically relevant hypotension incidences of 5% or 10% in the placebo group, the posterior probabilities of detecting an increase of 3-fold or 2.5-fold in incidence, respectively, are 82% and 80%, respectively. If there is no increase in clinically relevant hypotension, then the posterior probabilities of falsely detecting an increase are 13-15%. These probabilities do not reflect multiple comparison.

With regards to overall performance for selection of a maximally tolerated dose, a sample size of 50 per group for Part I (Cohort 1), along with 70 per group for Part II (Cohort 2) will identify a maximally tolerated dose approximately 50-70%, based on detecting an increase of 3-fold or 2.5-fold in incidence, and using sample decision rules that are consistent with above. Also, the design will provide an option to select a titrated 12 μg/kg/min dose approximately 60% of the time when that dose is tolerated, but a non-titrated 12 μg/kg/min dose is not tolerated. Conversely, the study design will not identify a maximally tolerated dose from Part II (Cohort 2) approximately 80%-85% of the time when no maximally tolerated dose exists

8.2 Populations for Analyses

- The Enrolled Subjects Data Set will consist of all subjects who sign informed consent
- The Randomized Subjects Data Set will consist of all randomized subjects who have started study drug infusion. This is also known as the Intent to Treat (ITT) population. Data in this data set will be analyzed based on randomized treatment group

- The Treated Subjects Data Set will consist of all subjects who receive any study drug infusion. This will be the primary safety data set. Data in this data set will be analyzed based on randomized treatment, except in the following cases:
    - If a subject received the same incorrect treatment throughout the 48 hours study drug infusion or until discontinuation of the study drug, then the subject will be analyzed based on the treatment received
    - If a subject received study drug from more than one treatment group, and none of the administrations were consistent with the assigned randomized treatment group, then the subject will be analyzed based on the first treatment received
- The Pharmacokinetic analysis dataset will consist of all subjects who receive BMS-986231 and have at least one post dose PK sample

8.3 Endpoints

8.3.1 Primary Endpoint

The primary endpoint is the incidence of clinically relevant hypotension, defined by SBP < 90 mm Hg (confirmed by a repeated value < 90 mm Hg) or symptoms of hypotension, up to 6 hours after the end of study drug infusion.

8.3.2 Secondary Endpoints

- Change in NT-proBNP from baseline to Hour 24, 48, 72, 120 or discharge (whichever comes first), and at Day 32
- Change in patient-reported resting dyspnea from baseline through Hour 72, as measured by the area under the curve (AUC) of the 11-point Numerical Rating Scale (NRS) obtained at baseline, and Hours 6, 12, 24, 48, and 72

8.3.4 Safety Endpoints.

Safety endpoints consist of the following:

- The incidence of symptomatic hypotension up to 6 hours after the end of study drug infusion
- The incidence of SBP < 90 mm Hg (confirmed by a repeated value)
- Change in Troponin T from baseline to Hour 24, 48, and 72
- Percentage of subjects who have died (all- cause and CV related) through Day 182

Additionally, the percentage of subjects with discontinuation due to symptomatic hypotension, as well as percentage of subjects with down-titrations, interruptions or discontinuations as a result of low blood pressure, either protocol specified clinically relevant hypotension, or asymptomatic decreases will be assessed. Other safety endpoints include the incidence of Adverse Events and Marked Laboratory Abnormalities, changes from baseline in vital signs, ECGs, physical measurements and laboratory assessments through Hour 120 or discharge, whichever comes first. The incidence of Serious Adverse Events will be assessed though Day 32.

8.4 Analyses

Results from Part I (Cohort 1) and Part II (Cohort 2) will be presented separately.

For analyses involving baseline, the baseline value is defined by the last value prior to the start of infusion, unless otherwise noted.

8.4.1 Demographics and Baseline Characteristics

Frequency distributions and summary statistics for demographic and baseline variables will be presented by treatment group and for all subjects combined. Demographic variables to be summarized include: age, gender, race, and geographic region.

Baseline variables to be summarized include physical measurements (height, body weight, body mass index), vital signs (systolic blood pressure, diastolic blood pressure, and heart rate), disease characteristics (New York Heart Association Class prior to admission, ejection fraction, heart failure etiology, number of heart failure hospitalizations in past year, time since original HF diagnosis and since first diuretic use in the current episode of decompensation to first treatment, commorbities, including history of coronary artery disease, hypertension, or diabetes, and presence of atrial fibrillation), important laboratory variables (including NT-proBNP, serum sodium and eGFR), and current heart failure medications.

8.4.2 Primary, Secondary, and Exploratory Endpoints Analyses

8.4.2.1 Primary Endpoint Analysis

The incidence of clinically relevant hypotension from the start to 6 hours after the end of study drug infusion will be summarized by treatment. Point estimates and 95% CIs for event rates will be presented by treatment, together with point estimates and 95% CIs for the risk difference and relative risk between each BMS-986231 arm and placebo.

8.4.2.2 Secondary Endpoint Analyses

NT-proBNP will be summarized descriptively by treatment for each time point, as well as change from baseline.

Analyses for changes from baseline in the resting dyspnea as measured by the 11-point NRS will be done using a longitudinal repeated measures model, with baseline value and region as covariates. A trapezoidal rule will be applied to calculate AUC using model-estimated values from the time points. Missing values for the dyspnea NRS will not be imputed, except if a NRS cannot be obtained because the subject has died or is physically unable to complete the form. In these cases, a worst score imputation will be used for that time point.

[redacted]

[redacted]

8.4.3 Safety Analyses

Troponin T will be summarized descriptively by treatment for each time point, as well as change from baseline.

Percentage of subjects who have died (all- cause and CV related) through Day 182 will be summarized descriptively by treatment.

All recorded adverse events 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.

Percentage of subjects with discontinuations due to symptomatic hypotension, as well as percentage of subjects with down-titrations or interruptions or discontinuations as a result of hypotension, either protocol specified clinically relevant hypotension, or asymptomatic decreases will be summarized descriptively by treatment.

In addition, the final infusion dose at the completion of 48 hours infusion will be summarized descriptively by treatment. The subjects who discontinued prematurely from infusion would be counted as having a final infusion dose of 0 μg/kg/min.

8.4.4 Pharmacokinetic Analyses

Blood samples will be collected from all subjects at 0.75, 4, 8, 14, and 48 hours during infusion and 4 hours after end of infusion and plasma concentrations will be measured using LC-MS. 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.

[redacted]

8.4.6 Outcomes Research Analyses

Healthcare utilization is defined as the percentage of subjects with rehospitalizations and emergency department visits will be summarized descriptively by treatment group for HF or other cardiovascular disease separately.

8.4.7 Other Analyses

Not applicable.

8.5 Interim Analyses

Two interim analyses will be performed for this study. An interim analysis will be performed following the completion of the last visit at Hour 120 in Part I (Cohort 1). The analysis will include data for all Cohort 1 subjects through at least Hour 120. The DMC, Executive Committee and representatives from the Sponsor will assess hypotension, as well as additional safety information, in addition to any available endpoint events. The outcome will determine whether 12 μg/kg/min is a sufficiently tolerated dose to be used in Part II (Cohort 2). The dose selection decision for Part II will be made by the Sponsor in collaboration with the Executive Committee, with input from the DMC. The doses for Part II (Cohort 2) will be determined based on general guiding principles and considered in the context of the totality of the data. For example, some of the critical information that will be considered evaluating the suitability 12 μg/kg/min for Part II will include the percentage of subjects completing the 48 hour infusion, percentage of subjects with temporary interruptions or permanent discontinuation of study drug, percentage of subjects with clinically relevant hypotension, percentage of subjects with symptomatic hypotension, and other key safety endpoints of interest (eg, renal function).

The second interim analysis will be performed following completion of the last visit at Day 32 in Part II (Cohort 2) in order to facilitate drug development decisions. The study analysis team will then provide top-line results to the project team.

After each DMC review, the Sponsor will be advised by the DMC Chair as to whether the study is safe to proceed as written, that the study should be modified, or that the study should be stopped. In addition to these periodic reviews, the DMC will review the unblinded data from Part I in parallel with the review by the executive committee and the Sponsor. A similar recommendation will be provided to the Sponsor, that the study is to proceed as written, or should be modified or stopped.

Analyses will consist of summaries of the available data. No formal inferences requiring any adjustment to statistical significance level will be performed

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

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

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

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

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority, must be sent to BMS. If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

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

9.1.2 Monitoring

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

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

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

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

9.1.2.1 Source Documentation

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

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

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

9.2 Records

9.2.1 Records Retention

The investigator (or head of 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 or designee 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.

9.2.2 Study Drug Records

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

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 subject, including unique subject identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number

If...	Then...
	• amount dispensed to and returned by each subject, including unique subject identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

9.2.3 Case Report Forms

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

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

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

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

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

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

9.3 Clinical Study Report and Publications

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

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

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

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

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraception's must be discussed in the event that the subject chooses to forego complete abstinence.
Presentation	First dose of IV diuretic for the current episode

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ADHF	acute decompensated heart failure
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	Aminotransaminases
AUC	area under the concentration-time curve
BiPAP	bilevel positive airway pressure
BMS	Bristol-Myers Squibb
BNP	brain natriuretic peptide
BP	blood pressure
bpm	Beats per minute
BUN	blood urea nitrogen
C	Celsius
CCU	coronary care unit
CFR	Code of Federal Regulations
CI	cardiac index
CPAP	continuous positive airway pressure
CRF	Case Report Form, paper or electronic
CVA	cerebral vascular accident
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Emergency Department
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
ESR	Expedited Safety Report
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
H	Hour
HF	heart failure

Term	Definition
HFrEF	heart failure with reduced ejection fraction
HNO	Nitroxyl
HRT	hormone replacement therapy
Hs	high sensitivity
IABP	Intra-Aortic Balloon Pump
ICH	International Conference on Harmonisation
ICU	intensive care unit
Ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous
K3EDTA	potassium ethylenediaminetetraacetic acid
Kg	Kilogram
LVEF	left ventricular ejection fraction
mg	Milligram
min	Minute
Mm Hg	millimeters of mercury
MS	mass spectrometry
MUGA	multigated acquisition
µg	Microgram
Na+	Sodium
NIMP	non-investigational medicinal products
NO	nitric oxide
NRS	numerical rating scale
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
PADP	Pulmonary Artery Diastolic Pressure
PC	peripheral capillary wedge pressure
PDE3	phosphodiesterase 3

Term	Definition
PDE5	phosphodiesterase type 5
PK	pharmacokinetics
PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cell
SAE	serious adverse event
TIA	transient ischemic attack
WOCBP	women of childbearing potential

APPENDIX 1 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

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

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

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

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

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

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

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

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

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

UNACCEPTABLE METHODS OF CONTRACEPTION

A. Periodic abstinence (calendar, symptothermal, post-ovulation methods)
B. Withdrawal (coitus interruptus)
C. Spermicide only
D. Lactation amenorrhea method (LAM)
E. Periodic abstinence (calendar, symptothermal, post-ovulation methods)
F. Withdrawal (coitus interruptus)
G. Spermicide only
H. Lactation amenorrhea method (LAM)
I. Progestogen only hormonal contraception associated with inhibition of ovulation or where inhibition of ovulation is not the primary mode of action
J. Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®
K. Intrauterine hormone-releasing system (IUS)
L. Diaphragm with spermicide
M. Cervical cap with spermicide
N. Vaginal sponge with spermicide
O. Male or female condom with or without spermicide*

[redacted]

APPENDIX 2 CORE AND EXTENDED ADME GENE LIST

Core ADME Gene List:

Gene Symbol	Full Gene Name	Class
ABCB1	ATP-binding cassette, sub-family B (MDR/TAP), member 1	Transporter
ABCC2	ATP-binding cassette, sub-family C (CFTR/MRP), member 2	Transporter
ABCG2	ATP-binding cassette, sub-family G (WHITE), member 2	Transporter
CYP1A1	cytochrome P450, family 1, subfamily A, polypeptide 1	Phase I
CYP1A2	cytochrome P450, family 1, subfamily A, polypeptide 2	Phase I
CYP2A6	cytochrome P450, family 2, subfamily A, polypeptide 6	Phase I
CYP2B6	cytochrome P450, family 2, subfamily B, polypeptide 6	Phase I
CYP2C19	cytochrome P450, family 2, subfamily C, polypeptide 19	Phase I
CYP2C8	cytochrome P450, family 2, subfamily C, polypeptide 8	Phase I
CYP2C9	cytochrome P450, family 2, subfamily C, polypeptide 9	Phase I
CYP2D6	cytochrome P450, family 2, subfamily D, polypeptide 6	Phase I
CYP2E1	cytochrome P450, family 2, subfamily E, polypeptide 1	Phase I
CYP3A4	cytochrome P450, family 3, subfamily A, polypeptide 4	Phase I
CYP3A5	cytochrome P450, family 3, subfamily A, polypeptide 5	Phase I
DPYD	dihydropyrimidine dehydrogenase	Phase I
GSTM1	glutathione S-transferase M1	Phase II
GSTP1	glutathione S-transferase pi	Phase II
GSTT1	glutathione S-transferase theta 1	Phase II
NAT1	N-acetyltransferase 1 (arylamine N-acetyltransferase)	Phase II
NAT2	N-acetyltransferase 2 (arylamine N-acetyltransferase)	Phase II
SLC15A2	solute carrier family 15 (H+/peptide transporter), member 2	Transporter
SLC22A1	solute carrier family 22 (organic cation transporter), member 1	Transporter
SLC22A2	solute carrier family 22 (organic cation transporter), member 2	Transporter
SLC22A6	solute carrier family 22 (organic anion transporter), member 6	Transporter
SLCO1B1	solute carrier organic anion transporter family, member 1B1	Transporter
SLCO1B3	solute carrier organic anion transporter family, member 1B3	Transporter
SULT1A1	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 1	Phase II
TPMT	thiopurine S-methyltransferase,	Phase II
UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1	Phase II
UGT2B15	UDP glucuronosyltransferase 2 family, polypeptide B15	Phase II
UGT2B17	UDP glucuronosyltransferase 2 family, polypeptide B17	Phase II
UGT2B7	UDP glucuronosyltransferase 2 family, polypeptide B7	Phase II

Extended ADME Gene List:

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

Gene Symbol	Full Gene Name	Class
GSTT2	glutathione S-transferase theta 2	Phase II
SLC10A1	solute carrier family 10 (sodium/bile acid cotransporter family), member 1	Transporter
SLC15A1	solute carrier family 15 (oligopeptide transporter), member 1	Transporter
SLC22A11	solute carrier family 22 (organic anion/cation transporter), member 11	Transporter
SLC22A8	solute carrier family 22 (organic anion transporter), member 8	Transporter
SLC7A5	solute carrier family 7 (cationic amino acid transporter, y+ system), member 5	Transporter
SLCO1A2	solute carrier organic anion transporter family, member 1A2	Transporter
SLCO2B1	solute carrier organic anion transporter family, member 2B1	Transporter
SULT1A2	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 2	Phase II
SULT1A3	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 3	Phase II
SULT1B1	sulfotransferase family, cytosolic, 1B, member 1	Phase II
UGT1A3	UDP glucuronosyltransferase 1 family, polypeptide A3	Phase II
UGT1A6	UDP glucuronosyltransferase 1 family, polypeptide A6	Phase II
UGT1A7	UDP glucuronosyltransferase 1 family, polypeptide A7	Phase II
UGT1A8	UDP glucuronosyltransferase 1 family, polypeptide A8	Phase II
UGT1A9	UDP glucuronosyltransferase 1 family, polypeptide A9	Phase II
UGT2A1	UDP glucuronosyltransferase 2 family, polypeptide A1	Phase II
UGT2B11	UDP glucuronosyltransferase 2 family, polypeptide B11	Phase II
UGT2B28	UDP glucuronosyltransferase 2 family, polypeptide B28	Phase II
UGT2B4	UDP glucuronosyltransferase 2 family, polypeptide B4	Phase II
ABCA1	ATP-binding cassette, sub-family A (ABC1), member 1	Transporter
ABCA4	ATP-binding cassette, sub-family A (ABC1), member 4	Transporter
ABCB11	ATP-binding cassette, sub-family B (MDR/TAP), member 11	Transporter

Gene Symbol	Full Gene Name	Class
ABCB4	ATP-binding cassette, sub-family B (MDR/TAP), member 4	Transporter
ABCB5	ATP-binding cassette, sub-family B (MDR/TAP), member 5	Transporter
ABCB6	ATP-binding cassette, sub-family B (MDR/TAP), member 6	Transporter
ABCB7	ATP-binding cassette, sub-family B (MDR/TAP), member 7	Transporter
ABCC1	ATP-binding cassette, sub-family C (CFTR/MRP), member 1	Transporter
ABCC10	ATP-binding cassette, sub-family C (CFTR/MRP), member 10	Transporter
ABCC11	ATP-binding cassette, sub-family C (CFTR/MRP), member 11	Transporter
ABCC5	ATP-binding cassette, sub-family C (CFTR/MRP), member 5	Transporter
ABCC6	ATP-binding cassette, sub-family C (CFTR/MRP), member 6	Transporter
ABCC8	ATP-binding cassette, sub-family C (CFTR/MRP), member 8	Transporter
ABCC9	ATP-binding cassette, sub-family C (CFTR/MRP), member 9	Transporter
ABCG1	ATP-binding cassette, sub-family G (WHITE), member 1	Transporter
ADH1A	alcohol dehydrogenase 1A (class I), alpha polypeptide	Phase I
ADH1B	alcohol dehydrogenase IB (class I), beta polypeptide	Phase I
ADH1C	alcohol dehydrogenase 1C (class I), gamma polypeptide	Phase I
ADH4	alcohol dehydrogenase 4 (class II), pi polypeptide	Phase I
ADH5	alcohol dehydrogenase 5 (class III), chi polypeptide,methionyl aminopeptidase 1	Phase I
ADH6	alcohol dehydrogenase 6 (class V)	Phase I
ADH7	alcohol dehydrogenase 7 (class IV), mu or sigma polypeptide	Phase I
ALDH1A1	aldehyde dehydrogenase 1 family, member A1	Phase I
ALDH1A2	aldehyde dehydrogenase 1 family, member A2	Phase I
ALDH1A3	aldehyde dehydrogenase 1 family, member A3	Phase I
ALDH1B1	aldehyde dehydrogenase 1 family, member B1	Phase I

Gene Symbol	Full Gene Name	Class
ALDH2	aldehyde dehydrogenase 2 family (mitochondrial)	Phase I
ALDH3A1	aldehyde dehydrogenase 3 family, memberA1	Phase I
ALDH3A2	aldehyde dehydrogenase 3 family, member A2	Phase I
ALDH3B1	aldehyde dehydrogenase 3 family, member B1	Phase I
ALDH3B2	aldehyde dehydrogenase 3 family, member B2	Phase I
ALDH7A1	aldehyde dehydrogenase 7 family, member A1	Phase I
ALDH8A1	aldehyde dehydrogenase 8 family, member A1	Phase I
ALDH9A1	aldehyde dehydrogenase 9 family, member A1	Phase I
AOX1	aldehyde oxidase 1	Phase I
ARNT	aryl hydrocarbon receptor nuclear translocator	Modifier
CBR1	carbonyl reductase 1	Phase I
CBR3	carbonyl reductase 3	Phase I
CDA	cytidine deaminase	Modifier
CYB5R3	cytochrome b5 reductase 3	Phase I
CYP11A1	cytochrome P450, family 11, subfamily A, polypeptide 1	Phase I
CYP11B1	cytochrome P450, family 11, subfamily B, polypeptide 1	Phase I
CYP11B2	cytochrome P450, family 11, subfamily B, polypeptide 2	Phase I
CYP17A1	cytochrome P450, family 17, subfamily A, polypeptide 1	Phase I
CYP1B1	cytochrome P450, family 1, subfamily B, polypeptide 1	Phase I
CYP20A1	cytochrome P450, family 20, subfamily A, polypeptide 1	Phase I
CYP20A1	cytochrome P450, family 20, subfamily A, polypeptide 1	Phase I
CYP21A2	cytochrome P450, family 21, subfamily A, polypeptide 2	Phase I
CYP24A1	cytochrome P450, family 24, subfamily A, polypeptide 1	Phase I

Gene Symbol	Full Gene Name	Class
CYP26A1	cytochrome P450, family 26, subfamily A, polypeptide 1	Phase I
CYP27A1	cytochrome P450, family 27, subfamily A, polypeptide 1	Phase I
CYP2A13	cytochrome P450, family 2, subfamily A, polypeptide 13	Phase I
CYP2A7	cytochrome P450, family 2, subfamily A, polypeptide 7	Phase I
CYP2C18	cytochrome P450, family 2, subfamily C, polypeptide 18	Phase I
CYP2F1	cytochrome P450, family 2, subfamily F, polypeptide 1	Phase I
CYP2J2	cytochrome P450, family 2, subfamily J, polypeptide 2	Phase I
CYP39A1	cytochrome P450, family 39, subfamily A, polypeptide 1	Phase I
CYP3A43	cytochrome P450, family 3, subfamily A, polypeptide 43	Phase I
CYP3A7	cytochrome P450, family 3, subfamily A, polypeptide 7	Phase I
CYP4B1	cytochrome P450, family 4, subfamily B, polypeptide 1	Phase I
CYP4F11	cytochrome P450, family 4, subfamily F, polypeptide 11	Phase I
CYP51A1	cytochrome P450, family 51, subfamily A, polypeptide 1	Phase I
EPHX2	epoxide hydrolase 2, cytoplasmic	Phase I
FMO1	flavin containing monooxygenase 1	Phase I
FMO2	flavin containing monooxygenase 2	Phase I
FMO4	flavin containing monooxygenase 4	Phase I
FMO5	flavin containing monooxygenase 5	Phase I
GPX2	glutathione peroxidase 2 (gastrointestinal)	Phase I
GPX3	glutathione peroxidase 3 (plasma)	Phase I
GPX7	glutathione peroxidase 7	Phase I
GSR	glutathione reductase	Phase I
GSTK1	glutathione S-transferase kappa 1	Phase II

Gene Symbol	Full Gene Name	Class
GSTM5	glutathione S-transferase M5	Phase II
GSTZ1	glutathione transferase zeta 1 (maleylacetoacetate isomerase)	Phase II
NNMT	nicotinamide N-methyltransferase	Phase II
NR1I2	nuclear receptor subfamily 1, group I, member 2	Modifier
NR1I3	nuclear receptor subfamily 1, group I, member 3	Modifier
PNMT	phenylethanolamine N-methyltransferase	Phase II
PON1	paraoxonase 1	Phase I
PON2	paraoxonase 2	Phase I
PON3	paraoxonase 3	Phase I
POR	P450 (cytochrome) oxidoreductase	Modifier
PPARD	peroxisome proliferative activated receptor, delta	Modifier
PPARG	peroxisome proliferative activated receptor, gamma	Modifier
RXRA	retinoid X receptor, alpha	Modifier
SLC10A2	solute carrier family 10 (sodium/bile acid cotransporter family), member 2	Transporter
SLC13A1	solute carrier family 13 (sodium/sulfate symporters), member 1	Transporter
SLC13A2	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 2	Transporter
SLC13A3	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 3	Transporter
SLC16A1	solute carrier family 16 (monocarboxylic acid Transporter), member 1	Transporter
SLC19A1	solute carrier family 19 (folate transporter), member 1	Transporter
SLC22A10	solute carrier family 22 (organic anion/cation transporter), member 10	Transporter
SLC22A12	solute carrier family 22 (organic anion/cation transporter), member 12	Transporter
SLC22A13	solute carrier family 22 (organic cation transporter), member 13	Transporter
SLC22A14	solute carrier family 22 (organic cation transporter), member 14	Transporter

Gene Symbol	Full Gene Name	Class
SLC22A15	solute carrier family 22 (organic cation transporter), member 15	Transporter
SLC22A16	solute carrier family 22 (organic cation transporter), member 16	Transporter
SLC22A17	solute carrier family 22 (organic cation transporter), member 17	Transporter
SLC22A18	solute carrier family 22 (organic cation transporter), member 18	Transporter
SLC22A18AS	solute carrier family 22 (organic cation transporter), member 18 antisense	Transporter
SLC22A3	solute carrier family 22 (extraneuronal monoamine transporter), member 3	Transporter
SLC22A4	solute carrier family 22 (organic cation transporter), member 4	Transporter
SLC22A5	solute carrier family 22 (organic cation transporter), member 5	Transporter
SLC22A7	solute carrier family 22 (organic anion transporter), member 7	Transporter
SLC22A9	solute carrier family 22 (organic anion/cation transporter), member 9	Transporter
SLC27A1	solute carrier family 27 (fatty acid transporter), member 1	Transporter
SLC28A1	solute carrier family 28 (sodium-coupled nucleoside transporter), member 1	Transporter
SLC28A2	solute carrier family 28 (sodium-coupled nucleoside transporter), member 2	Transporter
SLC28A3	solute carrier family 28 (sodium-coupled nucleoside transporter), member 3	Transporter
SLC29A1	solute carrier family 29 (nucleoside Transporter), member 1	Transporter
SLC29A2	solute carrier family 29 (nucleoside Transporter), member 2	Transporter
SLC2A4	solute carrier family 2 (facilitated glucose transporter), member 4	Transporter
SLC2A5	solute carrier family 2 (facilitated glucose/fructose transporter), member 5	Transporter
SLC5A6	solute carrier family 5 (sodium-dependent vitamin transporter)	Transporter
SLC6A6	solute carrier family 6 (neurotransmitter transporter, taurine), member 6	Transporter
SLC7A8	solute carrier family 7 (cationic amino acid transporter, y+ system), member 8	Transporter
SLCO1C1	solute carrier organic anion transporter family, member 1C1	Transporter
SLCO2A1	solute carrier organic anion transporter family, member 2A1	Transporter

Gene Symbol	Full Gene Name	Class
SLCO3A1	solute carrier organic anion transporter family, member 3A1	Transporter
SLCO4A1	solute carrier organic anion transporter family, member 4A1	Transporter
SLCO4C1	solute carrier organic anion transporter family, member 4C1	Transporter
SLCO5A1	solute carrier organic anion transporter family, member 5A1	Transporter
SLCO6A1	solute carrier organic anion transporter family, member 6A1	Transporter
SULT1C1	sulfotransferase family, cytosolic, 1C, member 1	Phase II
SULT1C2	sulfotransferase family, cytosolic, 1C, member 2	Phase II
SULT1E1	sulfotransferase family 1E, estrogen-preferring, member 1	Phase II
SULT2A1	sulfotransferase family, cytosolic, 2A, DHEA preferring, member 1	Phase II
SULT2B1	sulfotransferase family, cytosolic, 2B, member 1	Phase II
TAP1	transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	Transporter
UGT1A10	UDP glucuronosyltransferase 1 family, polypeptide A10	Phase II
UGT1A4	UDP glucuronosyltransferase 1 family, polypeptide A4	Phase II
UGT1A5	UDP glucuronosyltransferase 1 family, polypeptide A5	Phase II
UGT2B10	UDP glucuronosyltransferase 2 family, polypeptide B10	Phase II
ABCC13	ATP-binding cassette, sub-family C (CFTR/MRP), member 13	Transporter
ARSA	arylsulfatase A	Modifier
CAT	catalase	Modifier
CHST8	carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 8	Phase II
CYP19A1	cytochrome P450, family 19, subfamily A, polypeptide 1	Phase I
CYP26C1	cytochrome P450, family 26, subfamily C, polypeptide 1	Phase I
CYP27B1	cytochrome P450, family 27, subfamily B, polypeptide 1	Phase I
CYP2R1	cytochrome P450, family 2, subfamily R, polypeptide 1	Phase I

Gene Symbol	Full Gene Name	Class
CYP2S1	cytochrome P450, family 2, subfamily S, polypeptide 1	Phase I
CYP46A1	cytochrome P450, family 46, subfamily A, polypeptide 1	Phase I
CYP4A11	cytochrome P450, family 4, subfamily A, polypeptide 11	Phase I
CYP4F12	cytochrome P450, family 4, subfamily F, polypeptide 12	Phase I
CYP4F2	cytochrome P450, family 4, subfamily F, polypeptide 2	Phase I
CYP4F3	cytochrome P450, family 4, subfamily F, polypeptide 3	Phase I
CYP4F8	cytochrome P450, family 4, subfamily F, polypeptide 8	Phase I
CYP4Z1	cytochrome P450, family 4, subfamily Z, polypeptide 1	Phase I
CYP7B1	cytochrome P450, family 7, subfamily B, polypeptide 1	Phase I
CYP8B1	cytochrome P450, family 8, subfamily B, polypeptide 1	Phase I
DHRS13	dehydrogenase/reductase (SDR family) member 13	Phase I
DHRS2	dehydrogenase/reductase (SDR family) member 2	Phase I
GPX1	glutathione peroxidase 1	Phase I
GPX4	glutathione peroxidase 4 (phospholipid hydroperoxidase)	Phase I
GPX5	glutathione peroxidase 5 (epididymal androgen-related protein)	Phase I
GPX6	glutathione peroxidase 6 (olfactory)	Phase I
GSS	glutathione synthetase	Phase I
GSTCD	glutathione S-transferase, C-terminal domain containing	Phase II
HNF4A	hepatocyte nuclear factor 4, alpha	Modifier
HNMT	histamine N-methyltransferase	Phase II
HSD11B1	hydroxysteroid (17-beta) dehydrogenase 11	Phase I
HSD17B11	hydroxysteroid (17-beta) dehydrogenase 11	Phase I
HSD17B14	hydroxysteroid (17-beta) dehydrogenase 14	Phase I

Gene Symbol	Full Gene Name	Class
LOC731356	similar to dehydrogenase/reductase (SDR family) member 4 like 2	Phase I
MGST1	microsomal glutathione S-transferase 1	Phase II
MGST2	microsomal glutathione S-transferase 2	Phase II
MGST3	microsomal glutathione S-transferase 3	Phase II
MPO	myeloperoxidase	Modifier
NOS1	nitric oxide synthase 1 (neuronal)	Phase I
NOS2A	nitric oxide synthase 2A (inducible, hepatocytes)	Phase I
NOS3	nitric oxide synthase 3 (endothelial cell)	Phase I
PPARA	peroxisome proliferator-activated receptor alpha	Modifier
SERPINA7	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 7	Modifier
SLC7A7	solute carrier family 7 (cationic amino acid transporter, y+ system), member 7	Transporter
SOD1	superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	Modifier
SOD2	superoxide dismutase 2, mitochondrial	Modifier
SOD3	superoxide dismutase 3, extracellular precursor	Modifier
SULF1	sulfatase 1	Phase I
SULT4A1	sulfotransferase family 4A, member 1	Phase II
TAP2	transporter 2, ATP-binding cassette, sub-family B (MDR/TAP)	Transporter
UGT8	UDP glycosyltransferase 8 (UDP-galactose ceramide galactosyltransferase)	Phase II
XDH	xanthine dehydrogenase	Phase I
ADHFE1	alcohol dehydrogenase, iron containing, 1	Phase I
CHST1	carbohydrate (keratan sulfate Gal-6) sulfotransferase 1	Phase II
CHST10	carbohydrate sulfotransferase 10	Phase II
CHST11	carbohydrate (chondroitin 4) sulfotransferase 11	Phase II

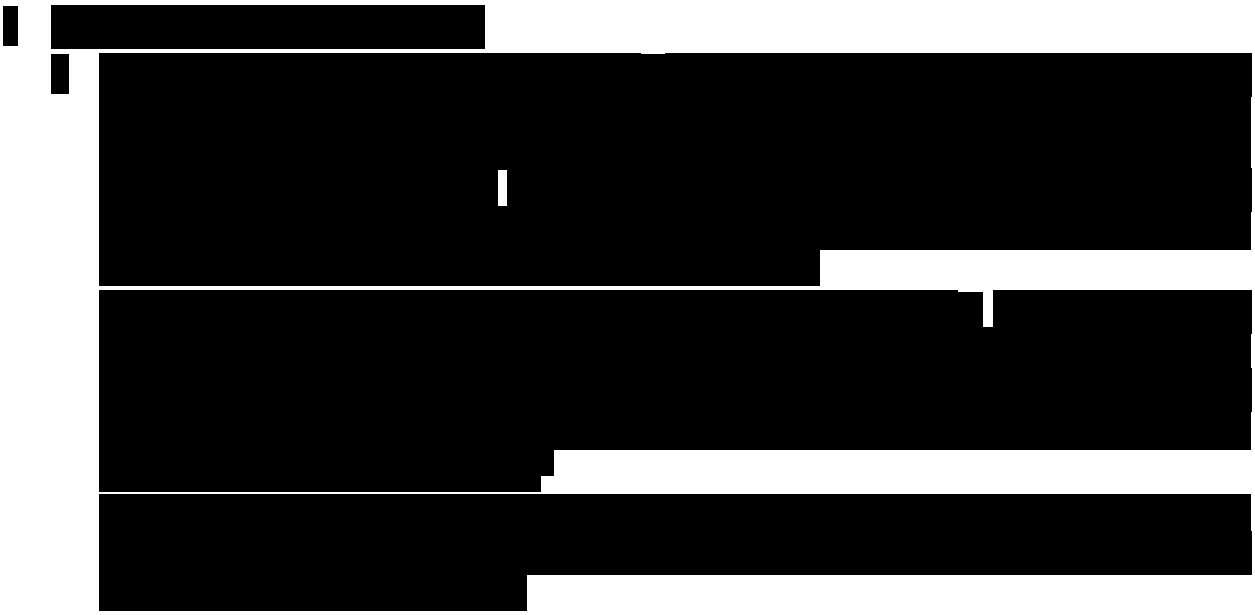
Gene Symbol	Full Gene Name	Class
CHST12	carbohydrate (chondroitin 4) sulfotransferase 12	Phase II
CHST13	carbohydrate (chondroitin 4) sulfotransferase 13	Phase II
CHST2	carbohydrate (N-acetylglucosamine-6-O) sulfotransferase 2	Phase II
CHST3	carbohydrate (chondroitin 6) sulfotransferase 3	Phase II
CHST4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

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

APPENDIX 3 COUNTRY SPECIFIC REQUIREMENTS

Regulations in Germany require that:

Inclusion criteria related to upper age limit of eligible participants and key exclusion criteria for anemia and hepatic function. Amendment also adds safety information about the Captisol® excipient being used and provides for an additional 24-hour ECG to be collected after treatment.



- Section 3.3.1, Inclusion Criteria, Age and Reproductive Status
  - a. Males and Females, at least age 18 (or age of majority), and no more than 85 years
- Section 3.3.2, Exclusion Criteria, Medical History and Concurrent Diseases
  - g. Severe liver disease defined as history of cirrhosis with evidence of portal hypertension such as varices, or encephalopathy, or total bilirubin > 3 mg/dL (> 51 mmol/L), or elevated AST or elevated ALT > 3 times ULN
- Section 3.3.2, Exclusion Criteria, Physical and Laboratory Test Findings
  - b. Have severe anemia, as documented by a hemoglobin < 10 g/dL (< 6.21 mmol/L)
- Section 4, Study Drug under Treatments
  - BMS will provide Investigational drug product BMS-986231 for infusion (active pharmaceutical ingredient BMS-986231 240 mg/vial formulated with Captisol® 3405 mg/vial) to all sites as per Table 4-1.
- Section 5.1, Flow Chart/Time and Events Schedule, Table 5.1-2
  - Addition of ECG at Hour 24 ± 2

[redacted]

Protocol Number: CV013011
IND Number: 118,618
Ex-US Non-IND
EUDRACT Number 2016-001685-29
Date: 28-Jun-2016
Revised Date: 24-Sep-2019

Clinical Protocol CV013011

A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Dose-Ranging, Phase 2b Study of the Safety and Efficacy of Continuous 48-Hour Intravenous Infusions of BMS-986231 in Hospitalized Patients with Heart Failure and Impaired Systolic Function

Revised Protocol 02c - Japan Specific

Study Director

[redacted]

Medical Monitor

Maria Borentain MD

[redacted]

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 02c	24-Sep-2019	Advise that Japan subjects who were enrolled after the end of global Part II enrollment will be followed for safety and rehospitalization endpoints through Day 32 only. The global study provides adequate safety follow up data and additional Day 182 data from the Japanese population is not necessary.
Revised Protocol 02b	30-May-2019	Additional blood pressure and heart rate measurements at 15 minutes, 45 minutes and 1.5 hours. Clarification that blood pressure measurements within ± 5 min in the first hour, then ± 15 min of the specified timepoints in Table 5.1-2.
Revised Protocol 02a	13-Mar-2019	Clarify the milestone, timing of enrollment and inclusion/exclusion criteria of the Japanese population. While the enrollment in the main study protocol will continue until 210 patients have been randomized globally in Part II (Cohort 2), enrollment in Japan may continue further only in Japan until approximately 18 total Japanese subjects are randomized.
Administrative Letter 04	02-Aug-2018	Clarified participation in the actigraphy and Holter monitoring sub-studies is optional for sites and patients. Furthermore, minor revisions are made to the PK Sampling schedule to reflect the required samples for Part II. In addition, a note is added to the 12-lead ECG procedure at hour 24 to clarify that it is only applicable to sites in Germany. Additional minor administrative corrections are also added.
Administrative Letter 03	27-Apr-2018	Corrected a typographical error in the "summary of key changes for revised protocol 02" table, which incorrectly noted the actigraphy and holter monitor sub-studies as exploratory endpoints. The actigraphy and holter monitor sub-studies are exploratory objectives.
Revised Protocol 02	09-Apr-2018	Expansion of screening period, addition of Holter Monitoring in a subset of patients, addition of Actigraphy monitoring in a subset of patients, and clarifications throughout the document.
Administrative Letter 02	05-Dec-2017	Clarifies secondary packaging of BMS986-231 as a carton containing 5 or 6 vials.
Administrative Letter 01	14-Feb-2017	Administrative clarifications throughout the protocol.
Revised Protocol 01	11-Oct-2016	Incorporates changes from Amendment 01.
Amendment 01	11-Oct-2016	Addition of two unblinded interim analysis, addition of Sensory Motor Survey, clarification and updates to Eligibility criteria, and additional edits throughout the document to improve readability.
Original Protocol	28-Jun-2016	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 02C:

The purpose of this amendment to advise that subjects in Japan who were enrolled after the end of global Part II enrollment will be followed for safety and rehospitalization endpoints through Day 32 only. The global study provides adequate safety follow up data and additional Day 182 data from the Japanese population is not necessary. A final analysis will be performed following completion of the last visit (Day 32) of the last enrolled Japanese subject to complete an analysis of the Japanese patient data. This revision applies to all subjects enrolled in Japan, excluding the subjects enrolled as part of the 210 subject global cohort (Part II, Cohort 2).

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02C

Section Number & Title	Description of Change	Brief Rationale
Synopsis & Section 1.3.4: Safety Objectives	Revise the Day 182 mortality follow-up safety objective: Assess the effect of BMS-986231 on mortality at Day 182, in the Global Cohorts only (including the Japanese subjects enrolled in Global Part II).	[redacted]
Figure 3.1-2 Study Design Schematic Part II (Cohort II)	Add note to schematic to specify that Day 32 follow up visit is the last visit for Subjects in Japan who were enrolled after the end of global Part II enrollment.	
Section 3.1: Study Design and Duration	Revise the following statements to distinguish Day 182 follow up for main study subjects from Day 32 follow up for subjects in Japan: The inpatient period will end in conjunction with the final in-patient assessment at Hour 120 or discharge, whichever comes first. All subjects enrolled as part of global Part II will be followed for	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02C		
Section Number & Title	**Description of Change**	**Brief Rationale**
	safety and rehospitalization endpoints through Day 32 and mortality through Day 182. Subjects in Japan who were enrolled after the end of global Part II enrollment will be followed for safety and rehospitalization endpoints through Day 32 For subjects in Japan who were enrolled after the end of global Part II, The end of trial is defined as the last subject's final follow-up visit on Day 32, or the last subject's scheduled procedure shown in the Time & Events schedule.	
Section 4.6.2: Other Blinding and Unblinding	Revise the below statement to include Day 32 follow up for subjects in Japan: The follow-up for Day 182 and/or Day 32 for both Part I and Part II will be site-and subject blinded	[redacted]
Table 5.1-3 Outpatient Follow-up (CV013011)	Revised to add the followed notes a and b: a: Subjects in Japan who were enrolled after the end of global Part II enrollment will be followed for safety and rehospitalization endpoints through Day 32. b: Day 182 Phone Visit not applicable for subjects in Japan who were enrolled after the end of global Part II enrollment, as they will be followed for safety and	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02C		
Section Number & Title	**Description of Change**	**Brief Rationale**
	rehospitalization endpoints through Day 32 only.	[redacted]
Synopsis & Section 5.7.3 Mortality	Revise the following statement to distinguish Day 182 follow up for main study subjects from Day 32 follow up for subjects in Japan: Investigators will follow all subjects in global part II to Day 182 for mortality. Subjects in Japan who were enrolled after the end of global Part II enrollment will be followed for through Day 32.	
Section 8.3.4: Safety Endpoints	Revise safety endpoint to remove reference to Day 182: Percentage of subjects who have died (all- cause and CV related)	
Section 8.4: Analyses	Revise statement below to add reference the Day 182 analysis: Subjects in Japan who started treatment after last patient randomization date of subjects who were enrolled before closure of the 210 subject global enrollment will not be part of the main global part II Day 32 interim analysis or the main global part II Day 182 analysis. Details will be provided in the statistical analysis plan	
Synopsis; Section 8.4.3: Safety Analyses	Revise the statement to remove reference to Day 182: Percentage of subjects who have died (all- cause and CV related) will be summarized descriptively by treatment.	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02C		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.5: Interim Analyses	Remove reference to an interim analysis in Japan, as one will not be completed.	[redacted]

SYNOPSIS

Clinical Protocol CV013011

Protocol Title: A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Dose-Ranging, Phase 2b Study of the Safety and Efficacy of Continuous 48-Hour Intravenous Infusions of BMS-986231 in Hospitalized Patients with Heart Failure and Impaired Systolic Function

Investigational Products, Dose and Mode of Administration, Duration of Treatment with Investigational Products: The investigational medicinal product is a solution for IV infusion containing BMS-986231 drug product (reconstituted in sterile water for injection), 5% dextrose (glucose) in water for injection (D5W) and potassium acetate (to achieve a 10 mM concentration of potassium acetate).

Study Phase: Phase 2B

Purpose: The purpose of this study is to evaluate the safety, tolerability, and efficacy of BMS-986231in subjects with heart failure (HF) and reduced systolic function (LVEF < 40%) who are admitted to the hospital with signs and symptoms of acute decompensated heart failure (ADHF).

Research Hypothesis: BMS-986231 is safe and tolerated with regard to clinically relevant hypotension compared with placebo in hospitalized heart failure with reduced ejection fraction (HFrEF) subjects with ADHF.

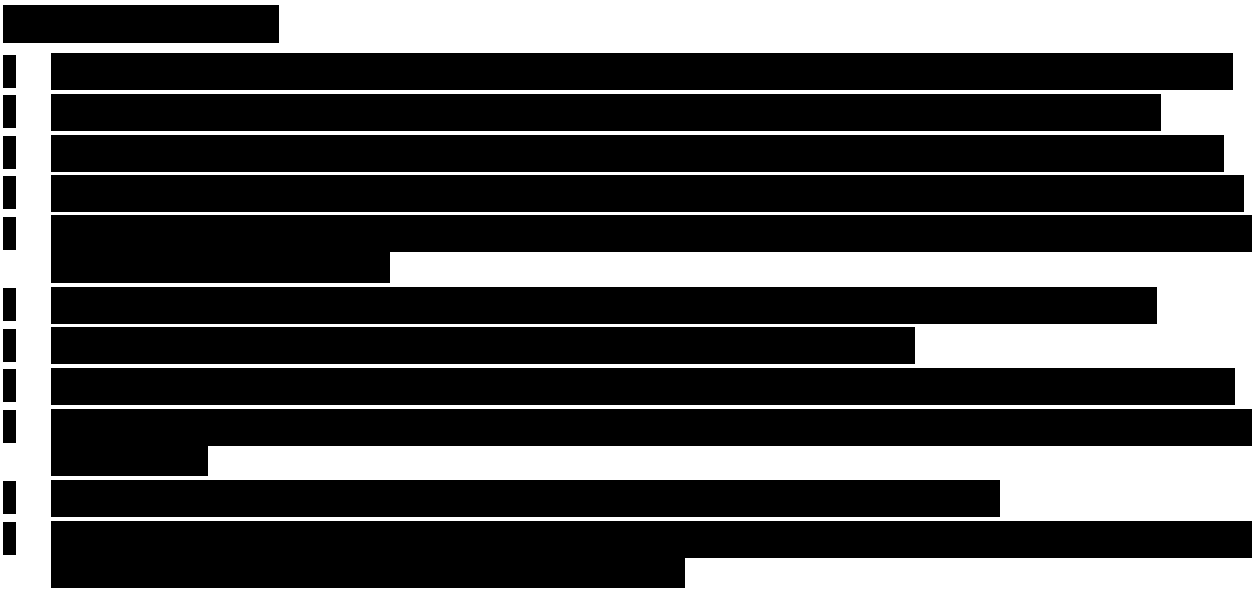
Objectives:

Primary Objective:

The primary objective is to evaluate the effects of various doses of BMS-986231 compared to placebo on clinically relevant hypotension (defined by SBP < 90 mm Hg or symptoms of hypotension)

Secondary Objectives:

- Assess the effect of BMS-986231 on NT-proBNP
- Assess the effect of BMS-986231 on patient-reported resting dyspnea as measured by the 11-point Numerical Rating Scale (NRS)



Safety Objectives:

- Evaluate the effect of BMS-986231 on incidence of symptomatic hypotension
- Evaluate the effects of BMS-986231 on the incidence of SBP < 90 mm Hg.
- Evaluate the incidence of dose reductions, temporary interruptions, and permanent discontinuation of BMS-98623 infusions
- Evaluate the safety and tolerability of a continuous 48-hour infusion of BMS-986231 in hospitalized HFrEF subjects with ADHF
- Evaluate the effect of BMS-986231 on high sensitivity (Hs) Troponin T
- Assess the effect of BMS-986231 on mortality at Day 182, in the Global Cohorts only (including the Japanese subjects enrolled in Global Cohort II)

Study Design: This is a multi-center, randomized, placebo-controlled, double-blind study of continuous 48-hour intravenous (IV) infusions of BMS-986231 in hospitalized HFrEF subjects with ADHF. The trial was designed to identify the doses of BMS-986231 that are safe and tolerated with regard to clinically relevant hypotension.

The study consists of 2 parts, each with a unique cohort of subjects.

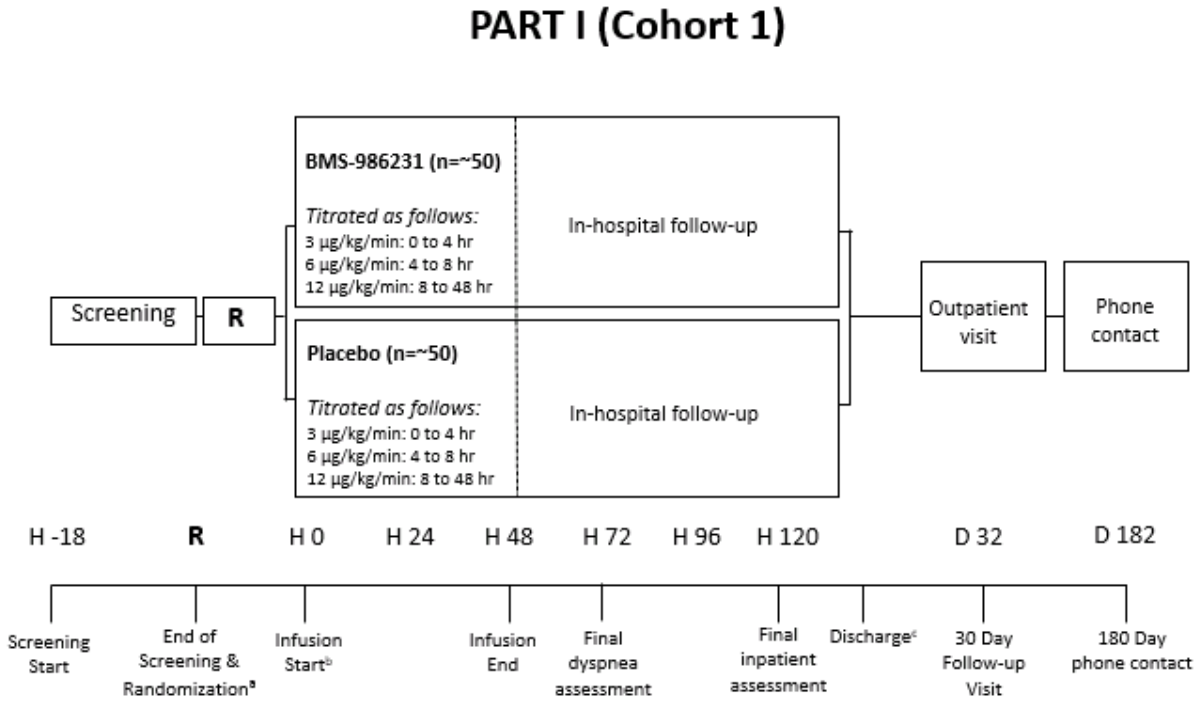
Patients that are randomized in Part I of the study will not be allowed to participate in Part II.

In Part I (Cohort 1) of the study, approximately 100 subjects will be randomized in a 1:1 ratio to placebo or an escalating dose of BMS-986231 (3 μg/kg/min for 4 hours, then 6 μg/kg/min for another 4 hours, then 12 μg/kg/min for the remaining 40 hours).

In Part II (Cohort 2) of the study, the 2 highest planned doses of BMS-986231 in Cohort 1, BMS-986231 6 μg/kg/min and BMS-986231 12 μg/kg/min, will be administered. Approximately 210 subjects will be randomized in a 1:1:1 ratio to one of the 2 active doses of BMS-986231 or placebo. If BMS-986231 12 μg/kg/min is not considered to be a tolerated dose in Part I, then BMS-986231 3 μg/kg/min and BMS-986231 6 μg/kg/min will be evaluated in Part II. In the event that neither 6 μg/kg/min nor 12 μg/kg/min are tolerated, the protocol will require modification.

While the enrollment in the main study protocol will continue until 210 patients have been randomized globally in Part II (Cohort 2), enrollment in Japan may continue further only in Japan until approximately 18 total Japanese subjects are randomized.

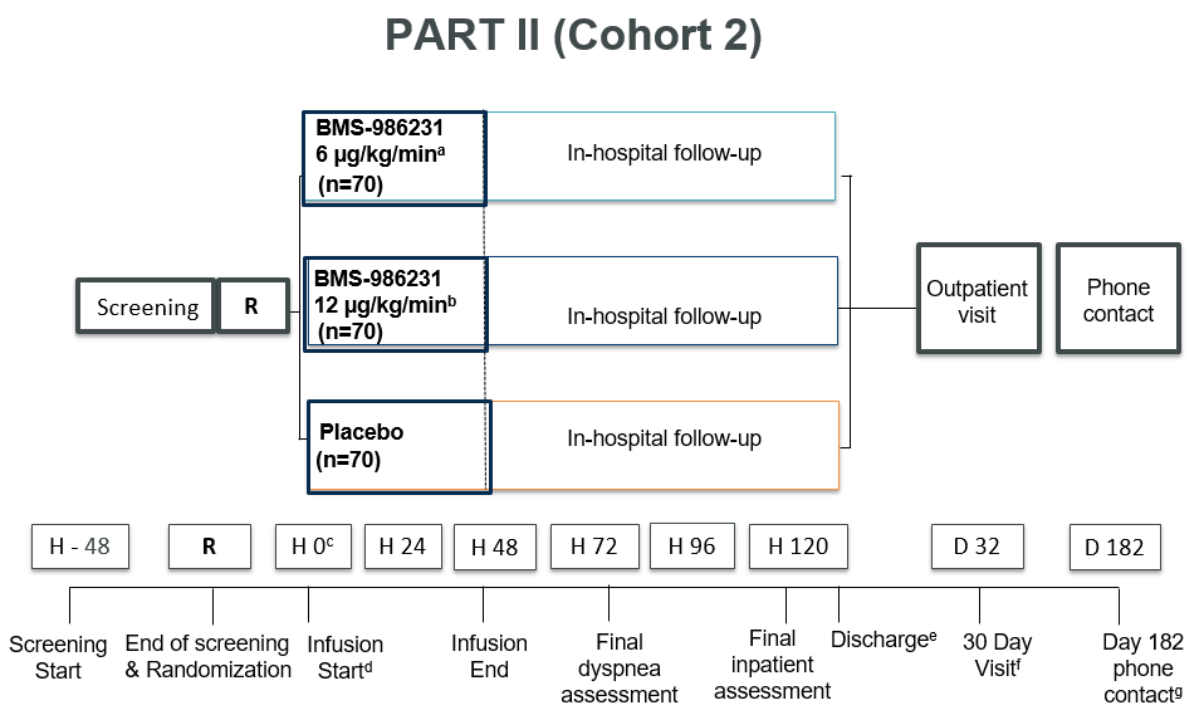
Study Schematic:



[a] Every effort should be made to initiate study drug administration promptly after randomization

[b] Study Medication infusion must start within 18 hours of presentation (or 48 hours in Part II Cohort 2 of the trial), defined as the first dose of diuretic for current episode, but not within 2 hours after an IV bolus dose of intravenous diuretics, or within 2 hours after the initiation or an increase in the dose of an IV diuretic administered by continuous infusion

[c] Discharge may occur as per standard medical practice. It is recommended that subjects remain in the hospital for at least 24 hours after the completion of the 48-hour infusion of study drug for safety monitoring



[a] 3 µg/kg/min if 12 µg/kg/min is not tolerated in Part I

[b] 6 µg/kg/min if 12 µg/kg/min is not tolerated in Part I

[c] Every effort should be made to initiate study drug administration promptly after randomization

[d] Study Medication infusion must start within 18 hours of presentation, (or 48 hours in Part II Cohort 2 of the trial) defined as the first dose of diuretic for current episode, but not within 2 hours after an IV bolus dose of intravenous diuretics, or within 2 hours after the initiation or an increase in the dose of an IV diuretic administered by continuous infusion

[e] Discharge may occur as per standard medical practice. It is recommended that subjects remain in the hospital for at least 24 hours after the completion of the 48-hour infusion of study drug for safety monitoring.

f Day 32 visit is the last visit for subjects in Japan who were enrolled after the end of global part II enrollment

g All subjects enrolled as part of global part II will be followed for mortality through Day 182

Study Population:

Key Inclusion Criteria:

- Males and Females, at least age 18 (or age of majority)
- Subjects being hospitalized for ADHF
- Have had at least 40 mg furosemide intravenous, or equivalent, (eg, 40 mg furosemide equivalent to 20 mg torsemide or to 1 mg bumetamide) for the current ADHF episode
- Subject must be randomized and treated within 18 hours of first dose of intravenous diuretic for Part I Cohort 1 (or 48 hours of first dose for Part II Cohort 2).
- Have dyspnea at rest or with minimal exertion after administration of at least 1 dose of intravenous diuretics. Subject must not be randomized within 2 hours after an IV bolus dose of intravenous diuretics, or within 2 hours after the initiation or a dose increase of an IV diuretic administered by continuous infusion
- Have a history of heart failure and a left ventricular ejection fraction (LVEF) $\leq 40\%$, as assessed by echocardiography, a multigated acquisition (MUGA) scan or magnetic resonance imaging (MRI) scan
  - Note: Ejection fraction documentation up to 18 months prior to screening may be used if there is no clinical expectation of improvement in ejection fraction in that timeframe (eg, the patient has not had biventricular pacing initiated during that period)
- Have at least 2 of the following at time of screening:
  - evidence for pulmonary congestion on chest x-ray
  - rales by chest auscultation
  - edema $\geq$ 2+ on a 0 to 3+ scale (easily identifiable indentation, skin rebounds in 15-30 seconds)
  - presence of jugular venous distention
- Have an elevated NT-proBNP $\geq$ 1400 pg/mL (166 pmol/L) or BNP$\geq$ 350 pg/mL (101 pmol/L) as determined at the local laboratory within 18 hours prior to the start of study drug infusion for Part I Cohort 1 (or 48 hours for Part II Cohort 2)
- For subjects with atrial fibrillation: NT-proBNP $\geq$ 2400 pg/ml or BNP $\geq$ 600 pg/ml
- Body weight $\geq$ 40 kg and < 140 kg at screening
- Women of childbearing potential must have negative serum or urine pregnancy test within 18 hours of start of drug for Part I Cohort 1 (or 48 hours for Part II Cohort 2)

Key Exclusion Criteria:

- Screening OR baseline systolic blood pressure (SBP) of <105mm Hg or >160mm Hg at screening and just prior to randomization
- Heart rate < 50 or >130 beats per minute (bpm) at screening and just prior to randomization
- Have 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: Functional mitral regurgitation, as well as restrictive mitral inflow pattern on echocardiography is not exclusionary
- Have a body temperature $\geq$ 38.5°C (101.3°F) at any time from screening to randomization
- Have an active infection requiring current IV anti-microbial treatment
- Considered clinically unstable for other conditions than acute heart failure, either because of acute coronary syndrome or ongoing arrhythmia (or be receiving concomitant parenteral therapy with any antiarrhythmic drugs), or other unstable non-cardiovascular disease
- Suspected acute lung disease (e.g. pneumonia or asthma) or severe chronic lung disease (e.g. severe chronic obstructive pulmonary disease, pulmonary fibrosis, patients with hypercapnia or requiring home oxygen therapy or chronic oral steroids.)
- Have a history of sudden cardiac death with resuscitation within the past 6 months

- Be 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
- Serious comorbid non-cardiovascular disease in which the life expectancy of the subject is < 6 months (eg, acute systemic infection – sepsis, metastatic cancer, or other serious illnesses)
- Severe 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)
- Prior cardiac or renal transplant
- Have persistent abnormal serum electrolytes not resolved before randomization, 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)
- Have severe renal insufficiency before randomization (and during the current hospitalization) defined as an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 [based on any standard limit and equation employed by the local lab, eg, Modification of Diet in Renal Disease (MDRD) equation]. For patients with eGFR values less than but close to 30 mL/min/1.73m^2 upon testing, retesting is allowed
- Subjects administered IV or transdermal nitrate therapy prior to randomization, except if all 3 of the following criteria are met:
  - Systolic blood pressure at screening or just prior to randomization is > 120 mm Hg AND
  - The IV nitroglycerin dose is < 100 µg/min (or isosorbide dinitrate < 3 mg/hour), AND
  - The infusion rate and dose has been unchanged for > 2 hours
- History of chronic or intermittent renal support therapy (hemodialysis, ultrafiltration, or peritoneal dialysis)
- Subjects treated during the current hospitalization with IV vasoactive drugs such as dopamine, dobutamine, enoximone, nesiritide, nitroprusside, levosimendan, amrinone , milrinone, carperitide or nicorandil prior to start of study drug infusion, or have an anticipated need to be treated with any of these agents during the study drug infusion
- Subjects receiving any mechanical ventilation at the time of screening
- Subjects receiving non-invasive ventilation (CPAP/BiPAP) < 2 hours prior to randomization
- Participation in an investigational clinical drug study within 30 days or 5 elimination half-lives, (whichever is longer) prior to randomization

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

Study Drug for CV013011		
Medication	**Potency**	**IP/Non-IP**
BMS-98623 For Injection	BMS-986231 240 mg/vial	IP
Potassium Acetate	2 mEq/mL (20mL/vial)	Non-IP

BMS will provide Investigational drug product BMS-986231 for infusion (active pharmaceutical ingredient BMS-986231 formulated with Captisol® 3405 mg/vial) to all sites. In addition, Potassium acetate is to be locally sourced by sites within the US and will be supplied to all ex-US sites.

Study Assessments:

Blood pressure assessment:

The primary endpoint of the study is the incidence of clinically relevant hypotension, defined by SBP < 90 mm Hg (confirmed by a repeated value < 90 mm Hg) or symptoms of hypotension, up to 6 hours after the end of study drug infusion. Thus hypotension will be assessed by collection of symptoms and blood pressure measurements.

Symptomatic hypotension is defined as the presence of both low SBP and symptoms (eg, lightheadedness, dizziness, etc.) due to low blood pressure.

Blood pressure measurements should be performed with the subject in a semi-recumbent (about a 30º angle) position, whenever possible.

Blood pressure will be measured as indicated in Table 5.1-2 within (± 5 min in the first hour then ± 0.25 (15 min)) of the specified time points. In addition, sites may perform measurements at intervals defined by institutional standard of care for subjects receiving vasodilators, but no less than what is described in Table 5.1-2.

If the study drug dose is modified (decreased, interrupted, resumed or discontinued), the frequency of blood pressure measurements will follow a more intensive schedule for up to 6 hours following the dose modification (see table below). Upon completion of the intensive schedule, measurements can be either resumed per the original schedule, or follow the discontinuation schedule if the drug is permanently discontinued.

Schedule of Blood Pressure Collection Following a Dose Modification

	30 minutes Post	**1 hour post**	**2 hours post**	**4 hours post**	**6 hours post**
Dose reduction	X	X	X	X	X
Dose interruption	X	X	X	X	
Dose resumption	X	X	X	X	X
Dose discontinuation	X	X	X	X	X

Details for management of low blood pressure are detailed in section 5.3.1

In addition to assessments of blood pressure, the Investigator will be asked to collect and assess signs and symptoms of low blood pressure.

Efficacy Outcome Measures: Efficacy assessments will include the following:

Patient assessments of dyspnea severity at rest as measured by the 11-point Numerical Rating Scale (NRS) scores at screening and at 0, 6, 12, 24, 48, 72, and 120 hours after the start of study drug infusion.

Patient assessments of dyspnea severity at rest, using the 7-point Likert scale at 6, 12, 24, 48, 72, and 120 hours after the start of study drug infusion.

Patient assessments of global clinical status using the 7-point Likert scale at 6, 12, 24, 48, 72, and 120 hours after the start of study drug infusion.

An investigator assessment of in-hospital worsening heart failure since the start of the study drug infusion based on signs and symptoms of worsening heart failure along with the need for initiation or intensification of intravenous treatment for heart failure such as diuretics, vasodilators, inotropes, and mechanical support (mechanical ventilation,

circulatory support, ultrafiltration or hemodialysis), as indicators of worsening heart failure, will be made at Hours 24, 48, 72, 96, and 120 or discharge, whichever comes first.

Mortality Measures:

Investigators will follow all subjects to in global part II Day 182 for mortality. Subjects in Japan who were enrolled after the end of global Part II enrollment will be followed for through Day 32.

Investigators will be asked to report deaths and categorize them as either cardiovascular or non-cardiovascular death. All deaths will be assumed to be cardiovascular unless a non-cardiovascular cause can be clearly provided. Below is guidance for Investigator classification:

Cardiovascular Death:

Cardiovascular death includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes.

Non-cardiovascular Death:

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

Statistical considerations

Sample size:

For Part I (Cohort 1), approximately 50 subjects per group will be randomized to placebo or an incremental dose of BMS-986231 (3 - 6 - 12 μg/kg/min). Under a sample decision rule (eg, observed doubling with more than a 4% difference) and assuming clinically relevant hypotension incidences of 5% or 10% in the placebo group, the posterior probabilities of detecting an increase of 4-fold or 3-fold in incidence, respectively, are 86% and 80%, respectively. If there is no increase in clinically relevant hypotension, then the posterior probabilities of falsely detecting an increase are 11-12%.

For Part II (Cohort 2), approximately 70 subjects per group will be randomized to placebo or one of the two active dose levels of BMS-986231. Under a sample decision rule (eg, observed 1.8-fold increase with more than a 3% difference) and assuming clinically relevant hypotension incidences of 5% or 10% in the placebo group, the posterior probabilities of detecting an increase of 3-fold or 2.5-fold in incidence, respectively, are 82% and 80%, respectively. If there is no increase in clinically relevant hypotension, then the posterior probabilities of falsely detecting an increase are 13-15%. These probabilities do not reflect multiple comparison.

With regards to overall performance for selection of a maximally tolerated dose, a sample size of 50 per group for Part I (Cohort 1), along with 70 per group for Part II (Cohort 2) will identify a maximally tolerated dose approximately 50-70%, based on detecting an increase of 3-fold or 2.5-fold in incidence, and using sample decision rules that are consistent with above. Also, the design will provide an option to select a titrated 12 μg/kg/min dose approximately 60% of the time when that dose is tolerated, but a non-titrated 12 μg/kg/min dose is not tolerated. Conversely, the study design will not identify a maximally tolerated dose from Part II (Cohort 2) approximately 80%-85% of the time when no maximally tolerated dose exists.

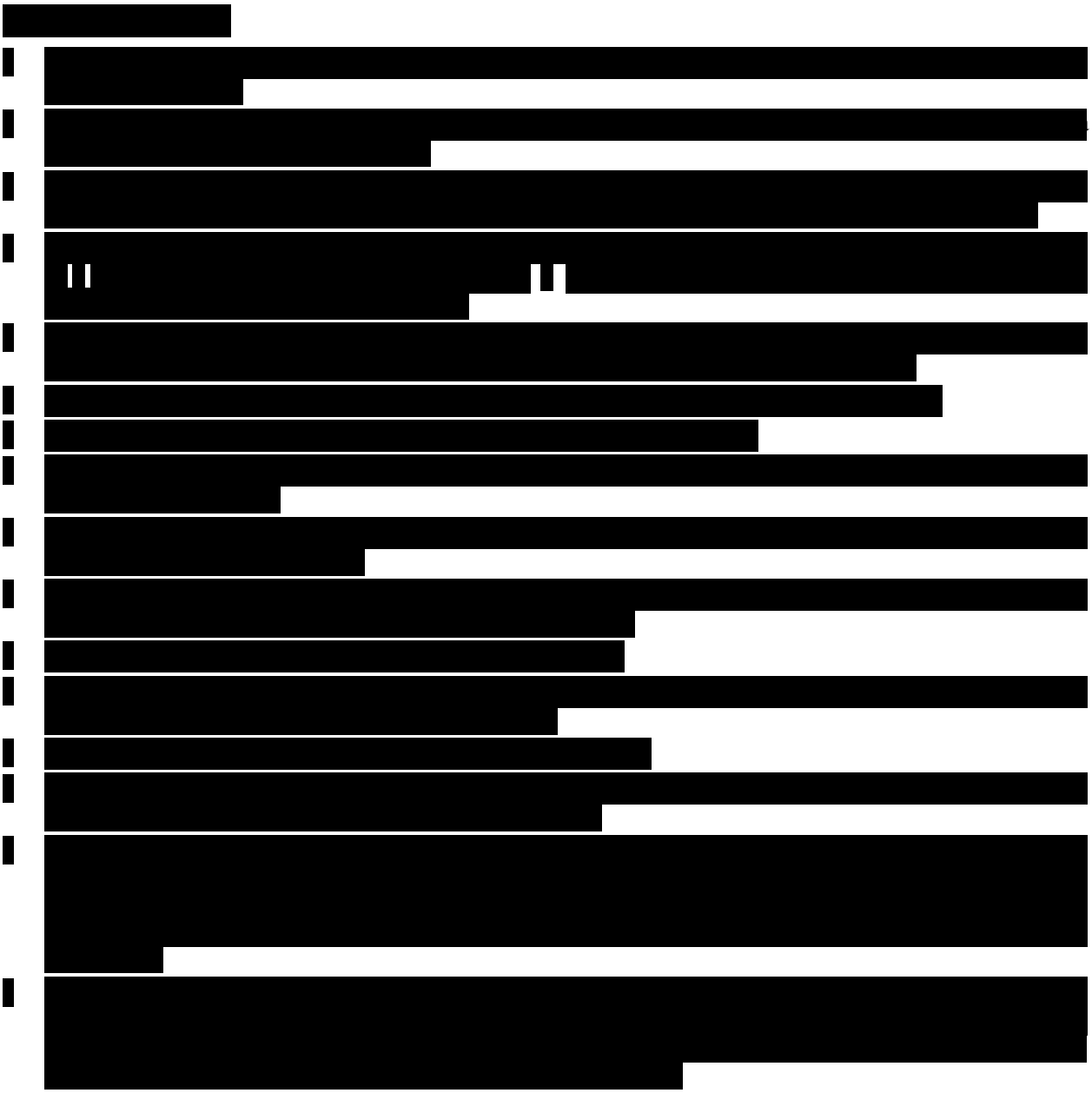
Endpoints:

Primary Endpoint:

The primary endpoint is the incidence of clinically relevant hypotension, defined by SBP < 90 mm Hg (confirmed by a repeated value < 90 mm Hg) or symptoms of hypotension, up to 6 hours after the end of study drug infusion.

Secondary Endpoints:

- Change in NT-proBNP from baseline to Hour 24, 48, 72, 120 or discharge, whichever comes first, and at Day 32
- Change in patient-reported resting dyspnea from baseline through Hour 72, as measured by the area under the curve (AUC) of the 11-point Numerical Rating Scale (NRS) obtained at baseline, and Hours 6, 12, 24, 48, and 72



Safety Endpoints

- The incidence of symptomatic hypotension up to 6 hours after the end of study drug infusion
- The incidence of SBP < 90 mm Hg (confirmed by a repeated value)
- Change in Troponin T from baseline to Hour 24, 48, and 72
- Percentage of subjects who have died (all- cause and CV related)

Additionally, the percentage of subjects with discontinuation due to symptomatic hypotension, as well as percentage of subjects with down-titrations, interruptions or discontinuations as a result of low blood pressure, either protocol specified clinically relevant hypotension, or asymptomatic decreases will be assessed. . Other safety endpoints include the incidence of Adverse Events and Marked Laboratory Abnormalities, changes from baseline in vital signs, ECGs,

physical measurements and laboratory assessments through Hour 120 or discharge, whichever comes first. The incidence of Serious Adverse Events will be assessed though Day 32.

Analyses: Results from Part I (Cohort 1) and Part II (Cohort 2) will be presented separately.

Subjects in Japan who started treatment after last patient randomization date of subjects who were enrolled before closure of the 210 subject global enrollment will not be part of the main global Part II Day 32 interim analysis or the main global Part II Day 182 analysis. Details will be provided in the statistical analysis plan

For analyses involving baseline, the baseline value is defined by the last value prior to the start of infusion, unless otherwise noted.

Primary Endpoint Analysis

The incidence of clinically relevant hypotension from the start to 6 hours after the end of study drug infusion will be summarized by treatment. Point estimates and 95% CIs for event rates will be presented by treatment, together with point estimates and 95% CIs for the risk difference and relative risk between each BMS-986231 arm and placebo.

Secondary Endpoint Analyses

NT-proBNP will be summarized descriptively by treatment for each time point, as well as change from baseline.

Analyses for changes from baseline in the resting dyspnea as measured by the 11-point NRS will be done using a longitudinal repeated measures model, with baseline value and region as covariates. A trapezoidal rule will be applied to calculate AUC using model-estimated values from the time points. Missing values for the dyspnea NRS will not be imputed, except if a NRS cannot be obtained because the subject has died or is physically unable to complete the form. In these cases, a worst score imputation will be used for that time point.

[redacted]

Safety Endpoint Analyses

Troponin T will be summarized descriptively by treatment for each time point, as well as change from baseline.

Percentage of subjects who have died (all- cause and CV related) will be summarized descriptively by treatment.

All recorded adverse events 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.

Percentage of subjects with discontinuations due to symptomatic hypotension, as well as percentage of subjects with down-titrations or interruptions or discontinuations as a result of hypotension, either protocol specified clinically relevant hypotension, or asymptomatic decreases will be summarized descriptively by treatment.

In addition, the final infusion dose at the completion of 48 hours infusion will be summarized descriptively by treatment. The subjects who discontinued prematurely from infusion would be counted as having a final infusion dose of 0 μg/kg/min.

Cardiodynamic ECG assessment (Subset of Subjects in Part II Cohort 2 only):

The analysis will be based on exposure-response modeling of the relationship between plasma concentrations of prodrug BMS-986231, its byproduct BMT-284730 and other metabolites (eg, BMT-279554 & CAR-000463) and change-from-baseline QTcF (ΔQTcF) with the intent to exclude an effect > 10 msec at clinically relevant plasma levels.

In addition, the effect of BMS-986231 on the placebo-corrected ΔQTcF (ΔΔQTcF) will be evaluated at each post-dosing time point ('by-time point' analysis) using the Intersection Union Test. An analysis of categorical outliers will be performed for changes in heart rate (HR), PR, QRS, QTcF, T-wave morphology and U-wave presence

Pharmacokinetic Analyses

Blood samples will be collected from all subjects at 0.75, 4, 8, 14, and 48 hours during infusion and 4 hours after end of infusion and plasma concentrations will be measured using LC-MS. 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.

TABLE OF CONTENTS

[redacted]

1.2 Research Hypothesis

BMS-986231 is safe and tolerated with regard to clinically relevant hypotension compared with placebo in hospitalized heart failure with reduced ejection fraction (HFrEF) subjects with ADHF.

1.3 Objectives

1.3.1 Primary Objective

The primary objective is to evaluate the effects of various doses of BMS-986231 compared to placebo on clinically relevant hypotension (defined by SBP < 90 mm Hg or symptoms of hypotension).

1.3.2 Secondary Objectives

- Assess the effect of BMS-986231 on NT-proBNP
- Assess the effect of BMS-986231 on patient-reported resting dyspnea as measured by the 11-point NRS)

[redacted]

[redacted]

1.3.4 Safety Objectives

- Evaluate the effect of BMS-986231 on incidence of symptomatic hypotension
- Evaluate the effects of BMS-986231 on the incidence of SBP < 90 mm Hg.
- Evaluate the incidence of dose reductions, temporary interruptions, and permanent discontinuation of BMS-98623 infusions.
- Evaluate the safety and tolerability of a continuous 48-hour infusion of BMS-986231 in hospitalized HFrEF subjects with ADHF
- Evaluate the effect of BMS-986231 on high sensitivity (Hs) Troponin T
- Assess the effect of BMS-986231 on mortality at Day 182, in the Global Cohorts only (including the Japanese subjects enrolled in Global Part II).

[redacted]

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

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

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

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

2.2 Institutional Review Board/Independent Ethics Committee

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

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

2.3 Informed Consent

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

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

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 subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study
- Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information
- If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject
- Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented

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

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a multi-center, randomized, placebo-controlled, double-blind study of continuous 48-hour intravenous (IV) infusions of BMS-986231 in hospitalized HFrEF subjects with ADHF. The trial was designed to identify the doses of BMS-986231 that are safe and tolerated with regard to clinically relevant hypotension.

The study consists of 2 parts, each with a unique cohort of subjects.

Subjects that are randomized in Part I of the study will not be allowed to participate in Part II.

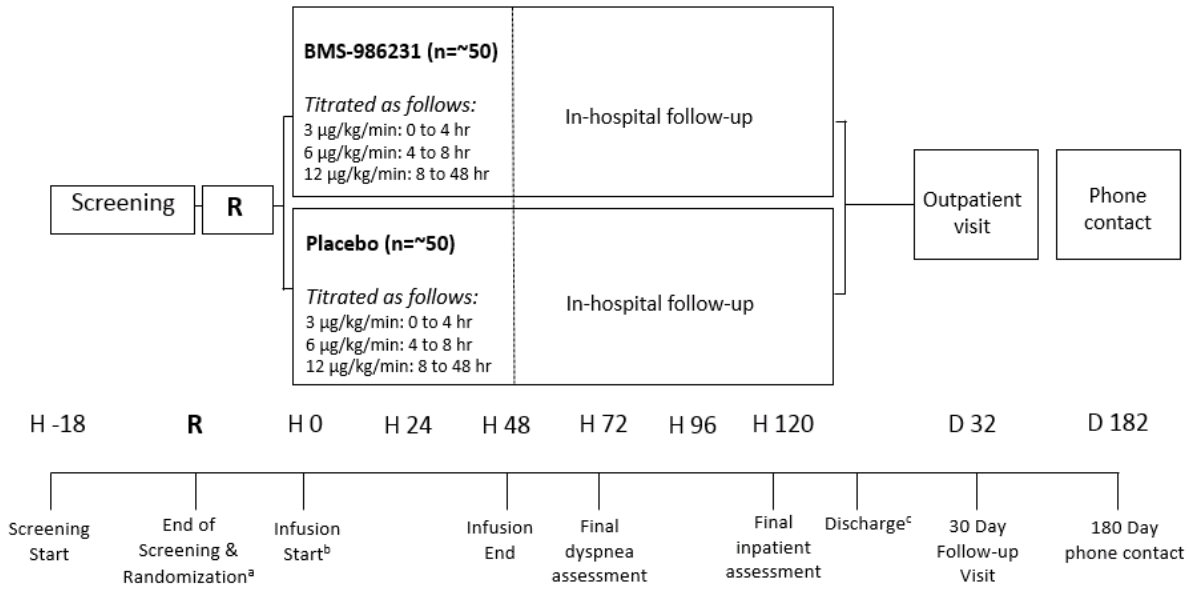
In Part I (Cohort 1) of the study, approximately 100 subjects will be randomized in a 1:1 ratio to an escalating dose of BMS-986231 (3 µg/kg/min for 4 hours, then 6 µg/kg/min for another 4 hours, then 12 µg/kg/min for the remaining 40 hours) or an escalating dose of placebo.

In Part II (Cohort 2) of the study, the 2 highest planned doses of BMS-986231 in Cohort 1, BMS-986231 6 µg/kg/min and BMS-986231 12 µg/kg/min, will be administered. Approximately 210 subjects will be randomized in a 1:1:1 ratio to one of the 2 active doses of BMS-986231 or placebo. If BMS-986231 12 µg/kg/min is not considered to be a tolerated dose in Part I, then BMS-986231 3 µg/kg/min and BMS-986231 6 µg/kg/min will be evaluated in Part II. In the event that neither 6 µg/kg/min nor 12 µg/kg/min are tolerated, the protocol will require modification.

While the enrollment in the main study protocol will continue until 210 patients have been randomized globally in Part II (Cohort 2), enrollment in Japan may continue further only in Japan until approximately 18 total Japanese subjects are randomized.

The study design schematic is presented in Figure 3.1-1 for Part I (Cohort 1) and Figure 3.1-2 for Part II (Cohort 2).

Figure 3.1-1: Study Design Schematic Part I (Cohort 1)

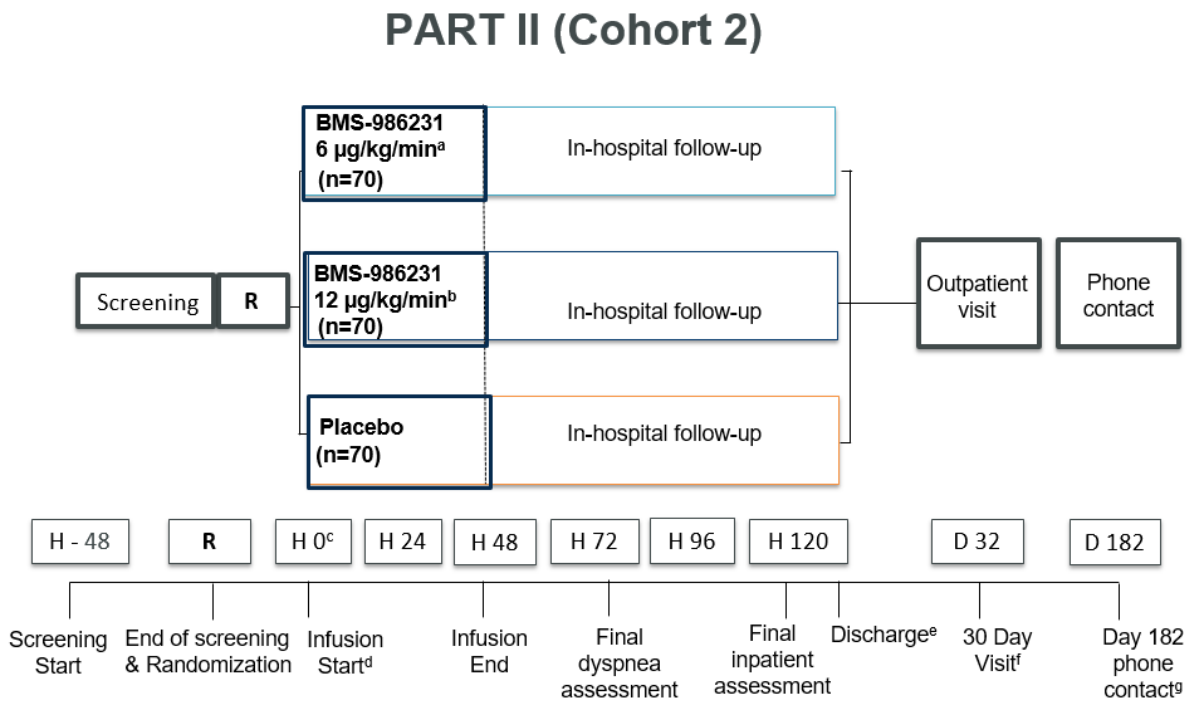


[a] Every effort should be made to initiate study drug administration promptly after randomization

[b] Study Medication infusion must start within 18 hours of presentation (or 48 hours in Part II Cohort 2 of the trial), with presentation defined as the first dose of diuretic for current episode, but not within 2 hours after an IV bolus dose of intravenous diuretics, or within 2 hours after the initiation or an increase in the dose of an IV diuretic administered by continuous infusion

[c] Discharge may occur as per standard medical practice. It is recommended that subjects remain in the hospital for at least 24 hours after the completion of the 48-hour infusion of study drug for safety monitoring

Figure 3.1-2: Study Design Schematic Part II (Cohort 2)



[a] 3 µg/kg/min if 12 µg/kg/min is not tolerated in Part I

[b] 6 µg/kg/min if 12 µg/kg/min is not tolerated in Part I

[c] Every effort should be made to initiate study drug administration promptly after randomization

[d] Study Medication infusion must start within 18 hours of presentation for Part I Cohort 1 (or 48 hours of presentation for Part II Cohort 2), with presentation defined as the first dose of diuretic for current episode, but not within 2 hours after an IV bolus dose of intravenous diuretics, or within 2 hours after the initiation or an increase in the dose of an IV diuretic administered by continuous infusion

[e] Discharge may occur as per standard medical practice. It is recommended that subjects remain in the hospital for at least 24 hours after the completion of the 48-hour infusion of study drug for safety monitoring.

[f] Day 32 visit is the last visit for subjects in Japan who were enrolled after the end of global part II enrollment

[g] All subjects enrolled as part of global part II will be followed for mortality through Day 182

Subjects must be randomized and treated within 18 hours of presentation for Part I Cohort 1 (or 48 hours of presentation for Part II Cohort 2). Presentation is defined as the first dose of IV diuretic for the current episode of ADHF. In addition, subjects must not be randomized within 2 hours following an IV bolus dose of diuretic, or within 2 hours after the initiation or an increase in the dose of an IV diuretic administered by continuous infusion. It is recommended that subjects remain in the hospital for at least 24 hours after the completion of the 48-hour infusion of study drug for safety monitoring.

Every effort must be made to initiate study drug administration promptly after randomization.

The inpatient period will end in conjunction with the final in-patient assessment at Hour 120 or discharge, whichever comes first.

The in-patient period will end in conjunction with the final in-patient assessment at Hour 120 or discharge, whichever comes first. All subjects enrolled as part of global part II will be followed for safety and rehospitalization endpoints through Day 32 and mortality through Day 182. Subjects in Japan who were enrolled after the end of global Part II enrollment will be followed for safety and rehospitalization endpoints through Day 32**.**

The start of the trial is defined as the first subject screened. End of trial is defined as the last subject's final follow-up visit on Day 182, or the last subject's scheduled procedure shown in the Time & Events schedule. For Subjects in Japan who were enrolled after the end of global Part II, The end of trial is defined as the last subject's final follow-up visit on Day 32, or the last subject's scheduled procedure shown in the Time & Events schedule.

3.2 Post Study Access to Therapy

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

3.3 Study Population

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

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

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

2) Target Population

a) Subjects being hospitalized for ADHF

b) Have had at least 40 mg furosemide intravenous, or equivalent (e.g 40 mg furosemide equivalent to 20 mg torsemide or to 1 mg bumetanide) for the current ADHF episode

c) Subject must be randomized and treated within 18 hours of first dose of intravenous diuretic for Part I Cohort 1 (or 48 hours of first dose for Part II Cohort 2).

d) Have dyspnea at rest or with minimal exertion after administration of at least 1 dose of intravenous diuretics. Subject must not be randomized within 2 hours after an IV bolus

dose of intravenous diuretics, or within 2 hours after the initiation or a dose increase of an IV diuretic administered by continuous infusion

e) Have a history of heart failure and a left ventricular ejection fraction (LVEF) ≤ 40%, as assessed by echocardiography, a multigated acquisition (MUGA) scan or magnetic resonance imaging (MRI) scan

   Note: Ejection fraction documentation up to 18 months prior to screening may be used if there is no clinical expectation of improvement in ejection fraction in that timeframe (eg, the patient has not had biventricular pacing initiated during that period)

f) Have at least 2 of the following at time of screening:
   i) evidence for pulmonary congestion on chest x-ray
   ii) rales by chest auscultation,
   iii) edema ≥ 2+ on a 0 to 3+ scale (easily identifiable indentation, skin rebounds in 15-30 seconds)
   iv) presence of jugular venous distention

g) Have an elevated NT-proBNP ≥ 1400 pg/mL (166 pmol/L) or BNP ≥ 350 pg/mL (101 pmol/L) as determined at the local laboratory within 18 hours prior to the start of study drug infusion for Part I Cohort 1 (or 48 hours for Part II Cohort 2)

   For subjects with atrial fibrillation: NT-proBNP ≥ 2400 pg/ml or BNP ≥ 600 pg/ml

h) Body weight ≥ 40 kg and < 140 kg at screening

i) Subject Re-Screening: This study permits the re-screening of a subject that has discontinued the study as a screen failure (has not been randomized). See Section 5.1.1 for more details

3) Age and Reproductive Status

a) Males and Females, at least age 18 (or age of majority) (Germany only, see Appendix 3)

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 18 hours prior to the start of study treatment for Part I Cohort 1 (or 48 hours for Part II Cohort 2)

c) Women must not be breastfeeding

d) WOCBP must agree to follow instruction for methods of contraception for 32 days after discontinuation (duration of study drug plus 30 days duration of one ovulatory cycle)

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for 92 days after discontinuation (duration of study drug plus 90 days (duration of sperm turnover)

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

Investigators shall counsel WOCBP, and male subjects 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 1), 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.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Systolic blood pressure (SBP) < 105 mm Hg or > 160 mm Hg at screening

b) Systolic blood pressure (SBP) < 105 mm Hg or > 160 mm Hg just prior to randomization

c) Heart rate < 50 beats per minute (bpm) or > 130 bpm at screening

d) Heart rate < 50 beats per minute (bpm) or > 130 bpm just prior to randomization

e) Have 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: Functional mitral regurgitation, as well as restrictive mitral inflow pattern on echocardiography is not exclusionary

f) Have a body temperature ≥ 38.5°C (101.3°F) at any time from screening to randomization

g) Have an active infection requiring current IV anti-microbial treatment

2. **Medical History and Concurrent Diseases**

a) Considered clinically unstable for other conditions than acute heart failure, either because of acute coronary syndrome or ongoing arrhythmia (or be receiving concomitant parenteral therapy with any antiarrhythmic drugs), or other unstable non-cardiovascular disease

b) Suspected acute lung disease (e.g. pneumonia or asthma) or severe chronic lung disease (e.g. severe chronic obstructive pulmonary disease, pulmonary fibrosis, patients with hypercapnia or requiring home oxygen therapy or chronic oral steroids.)

c) Have a history of sudden cardiac death with resuscitation within the past 6 months

d) Be hospitalized with acute coronary syndrome, coronary revascularization or acute myocardial infarction during the previous 90 days prior to screening

e) 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

f) Serious comorbid noncardiovascular disease in which the life expectancy of the subject is < 6 months (eg, acute systemic infection – sepsis, metastatic cancer, or other serious illnesses)

g) Severe 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) (Germany only, see Appendix 3)

h) Prior cardiac or renal transplant

3. Physical and Laboratory Test Findings

a) Have persistent abnormal serum electrolytes not resolved before randomization, as defined by any of the following:
   i) A sodium (Na+) concentration < 130 or >145 mEq/L (mmol/L)
   ii) A potassium (K+) concentration < 3.2 or >5.5 mEq/L (mmol/L)

b) Have severe anemia, as documented by a hemoglobin < 9 g/dL (< 5.59 mmol/L) (Germany only, see Appendix 3)

c) Have severe renal insufficiency before randomization (and during the current hospitalization) defined as an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 [based on any standard limit and equation employed by the local lab, eg, Modification of Diet in Renal Disease (MDRD) equation]. For patients with eGFR values less than but close to 30 mL/min/1.73m^2 upon testing, retesting is allowed.

4. Prior and Concomitant Medications or Treatments

a) Subjects administered IV or transdermal nitrate therapy prior to randomization, except if all 3 of the following criteria are met:
   i) Systolic blood pressure at screening or just prior to randomization is > 120 mm Hg **AND**
   ii) The IV nitroglycerin dose is < 100 μg/min (or isosorbide dinitrate < 3 mg/hour), AND
   iii) The infusion rate and dose has been unchanged for > 2 hours

b) History of chronic or intermittent renal support therapy (hemodialysis, ultrafiltration, or peritoneal dialysis)

c) Subjects treated during the current hospitalization with IV vasoactive drugs such as dopamine, dobutamine, enoximone, nesiritide, nitroprusside, levosimendan, amrinone or milrinone, carperitide or nicorandil prior to start of study drug infusion, or have an anticipated need to be treated with any of these agents during the study drug infusion

d) Subjects treated with oral phosphodiesterase type 5 (PDE5) inhibitor sildenafil, vardenafil or avanafil within 24 hours of screening or treated with tadalafil within 4 days of screening, oral inotropic agents (eg, pimobendan) or oral vasopressin V2 receptor antagonist (eg, tolvaptan) initiated for the current ADHF episode. NOTE: chronic use of tolvaptan is not exclusionary.

e) Subjects receiving any mechanical ventilation at the time of screening

f) Subjects receiving non-invasive ventilation (CPAP/BiPAP) < 2 hours prior to randomization

5. Allergies and Adverse Drug Reaction

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

6. Other Exclusion Criteria

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

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

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

3.3.3 Women of Childbearing Potential

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

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

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

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

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

- Initiation of PDE5 inhibitors or pimobendan is prohibited during study drug infusion and 24 hours after the end of the study drug
- The use of nitrates, except for subjects receiving stable IV dose of nitrates at randomization, should be avoided, unless clinically indicated (ie, episodes of angina, worsening HF)
- Administration of IV vasoactive drugs (such as dopamine, dobutamine, enoximone, nitroprussiate, levosimendan or milrinone) should be discouraged unless clinically warranted

(ie, if patient's status requires use of vasoactive treatments for conditions such as worsening heart failure)

3.4.2 Other Restrictions and Precautions

Not applicable.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

The below discontinuation criteria apply to both Part I (Cohort 1) and Part II (Cohort 2) of the trial.

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

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- If study medication has been interrupted for low blood pressure, resumed, and an episode of hypotension (or symptoms of hypotension) reoccurs (see Section 4.5.1)

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

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

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

3.6 Post Study Drug 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 subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or

survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

3.6.1 Withdrawal of Consent

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

3.6.2 Lost to Follow-Up

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

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

4 STUDY DRUG

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

Treatments:

BMS will provide Investigational drug product BMS-986231 for infusion (active pharmaceutical ingredient BMS-986231 formulated with Captisol® 3405 mg/vial) to all sites as per Table 4-1. In addition, Potassium acetate is to be locally sourced by sites within the US and will be supplied to all ex-US sites as per Table 4-1.

Table 4-1: Study Drugs for CV013011 - Part I (Cohort 1) and Part II (Cohort 2)

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-986231 For Injection	BMS-986231 240 mg/vial	IP	Open Label	White to pale yellow whole or fragmented cake in a 20 mL glass vial with Fluortec™ stopper and a blue flip-off aluminum cap. Secondary packaging is a carton containing 5 or 6 vials.	2 to 8°C (36-46°F) Store in original package, protect from light.
Potassium Acetate Injection, USP[a]	2 mEq/mL (20mL/vial)	Non-IMP	Open Label	Colorless solution in a 20 mL fliptop glass vial. Secondary packaging is a carton containing 6 vials	Store at 20 to 25°C (68 to 77°F).

[a] Supplied by BMS only to ex-US sites

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

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

Study medication will be prepared by an unblinded pharmacist (or appropriate designee) at time of randomization. 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.

4.2 Non-Investigational Product

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

In this study, the required Potassium Acetate used in the active and placebo infusions is considered non-investigational product.

4.3 Storage of Study Drug

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS and listed in Table 4-1 and drug product label. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and BMS contacted immediately.

Please refer to Pharmacy Manual for additional guidance on storage of study drug. Study drug not supplied by BMS will be stored in accordance with the package insert. Please refer to Section 9.2.2 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.

4.4 Method of Assigning Subject Identification

At the time of screening for both Part I (Cohort 1) and Part II (Cohort 2), each subject will be assigned a unique sequential subject number by interactive response technology (IRT). The IRT will be available 24 hours per day, 7 days a week. The subject number will consist of a unique

5 digit number which is assigned sequentially within a study (starting with 00001) by the IRT. This number will be used for identification throughout the study and will not be used for any other subject. Subjects screened for Part I, (Cohort 1) will be assigned sequential study numbers beginning with 00001, and subjects screened for Part II, (Cohort 2) will be assigned sequential study numbers beginning with 10001.

Randomization schedules will be generated by BMS and kept by the IRT vendor. Subjects who meet the inclusion/exclusion criteria will be randomly assigned by the IRT to placebo or an incremental dose of BMS-986231 (3 - 6 - 12 µg/kg/min) in a 1:1 ratio for Part I (Cohort 1) and placebo or 1 of the 2 active dose levels of BMS-986231 in a 1:1:1 ratio for Part II (Cohort 2).

Randomization will be stratified by region.

4.5 Selection and Timing of Dose for Each Subject

Subjects will be administered study medication as a continuous IV infusion over 48 hours.

Body weight measured at screening will be used for dose calculations.

Every effort must be made to initiate study drug administration promptly after randomization.

See Pharmacy Manual for additional dosing information.

4.5.1 Dose Reductions, Temporary Interruptions, and Permanent Discontinuations of Study Drug Due to Blood Pressure

Any decision to lower the dosage level of study drug or discontinue study drug should be based on the Investigators assessment of the subject's overall clinical stability, in the context of appropriate ongoing monitoring of the subject's condition. A 50% dosage adjustment downward maybe be achieved by decreasing the rate of study drug infusion.

In Part I (Cohort 1) subjects who require a dose reduction or temporary interruption during the first infusion period, hours 0 to 4 (dose of 3 µg/kg/min), will be permanently discontinued from study drug.

Study drug infusion rate may be reduced by 50%, temporarily interrupted, or permanently discontinued. See Figure 4.5.1-1 and the following sections for more detail.

Dose Reduction:

- If the subject experiences SBP < 95 mm Hg, without symptoms related to hypotension, the measurement must be repeated within 15 minutes. If the SBP remains < 95 mm Hg, the dose reduction must occur
- A 50% dosage adjustment downward may be achieved by decreasing the rate of study drug infusion by half
- After a dose reduction, the dose cannot be increased again

Temporary interruption:

- If the systolic blood pressure reduces below < 85 mm Hg, and remains < 85 mm Hg during a repeated measure within 15 minutes, the study drug must be interrupted for at least 1 hour
- For subjects that report symptoms consistent with hypotension (eg, dizziness, lightheadedness, etc.), and are related to hypotension, study drug must be interrupted for at least 1 hour

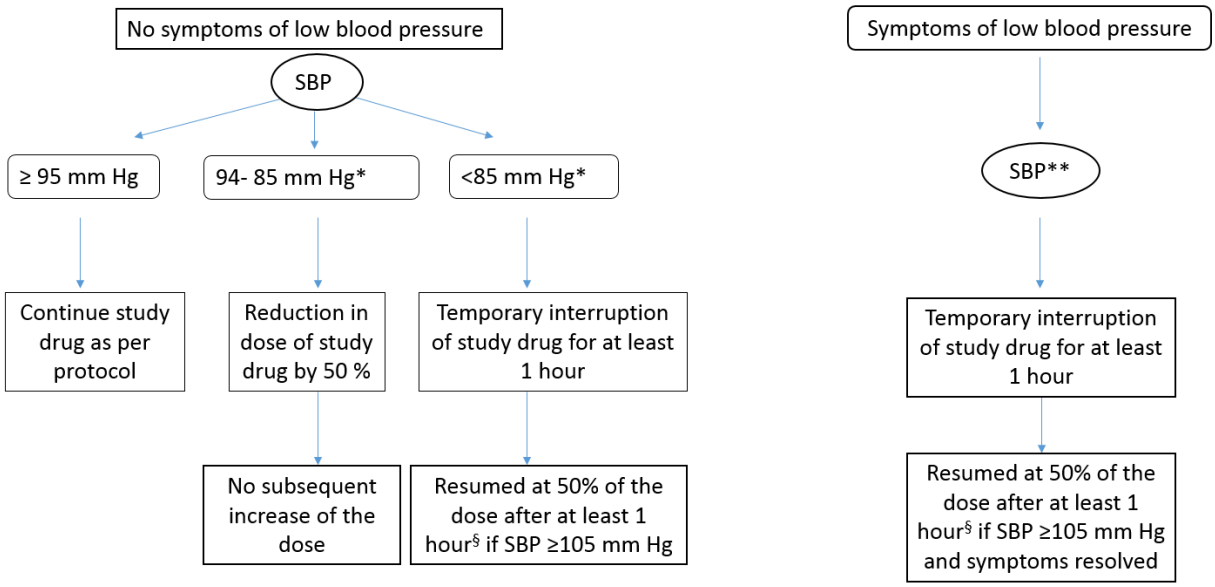
Resuming Study Drug

- Study drug may be resumed at 50% of the dose after 1 hour interruption, if SBP rises to values ≥ 105 mm Hg and any symptoms of hypotension, if present, have resolved.
- If after 4 hours, the subject's SBP remains below < 105 mm Hg, or if symptoms persist, then study drug must be permanently discontinued
- After a dose reduction, the dose cannot be increased again

Permanent discontinuation of the infusion:

- At any time during the administration of study drug, the study drug infusion must be discontinued if an AE or any other safety issue suggests it is not in the subject's best interest to continue to receive study drug
- Study drug will be permanently discontinued after it has been down titrated once, and criteria for dose reduction or interruption has been met again.

Figure 4.5.1-1: Guidance for Dose Reduction Based on Blood Pressure Measurements and/or Symptoms of low blood pressure



* Confirmed by a second measure within 15 min

** No need to wait for confirmatory measures within 15 min

§ But no more than 4 hours

4.6 Blinding/Unblinding

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

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

For this study, the method of unblinding for emergency purposes is 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 subject for non-emergency purposes should be discussed with the Medical Monitor.

4.6.2 Other Blinding and Unblinding

The Data Monitoring Committee (DMC; see Section 7) will assess safety on an ongoing basis, and will have access to unblinded treatment codes for individual subjects. An analysis team, including a reporting statistician and programming support, who are not involved with the conduct of the study, will provide analyses to the DMC.

Two interim analyses will be performed in this study.

The first unblinded interim analysis will be performed by the analysis team at the completion of the last visit at Hour 120 in Part I (Cohort 1). This analysis will be reviewed by the DMC and will be reviewed in parallel and by the executive committee (see Section 7) and Sponsor representatives. The rationale for a fully unblinded review by the executive committee and Sponsor is to determine whether 12 µg/kg/min is an appropriate dose to study in Part II.

The second interim analysis will be performed when 210 randomized subjects reach the last visit at Day 32 in Part II (Cohort 2). The study analysis team will then provide top-line results to the project team.

The follow-up to Day 182 and/or Day 32 for both Part I and Part II will be site-and-subject blinded.

Japanese subjects enrolled as part of the 210 subject global cohort (Part II, Cohort 2) will be site-and-subject blinded until the end of the study in Japan.

The Bioanalytical Sciences section or its designate may be unblinded to the randomized treatment assignments in order to minimize unnecessary assays of samples from control group subjects. Likewise, the Biotransformation section or its designate may be unblinded, if metabolite profiling work is conducted.

In certain circumstances a pharmacokineticist or designates in Clinical Pharmacology and Pharmacometrics, biostatisticians and programmers 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 assignments.

The pharmacist at the site and/or its designate will be unblinded to the randomized treatment assignments in order to dispense treatment from bulk supplies, as needed. An unblinded Site Monitor, not involved with other study conduct, will be assigned exclusively to reconcile study medication and assure accountability.

Except as noted above, other members of BMS Research and Development personnel, as well as all vendors responsible for the conduct of the trial (protocol team) will remain blinded.

4.7 Treatment Compliance

Not applicable.

4.8 Destruction or Return of Investigational Product

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

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

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

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

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

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

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

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

4.9 Retained Samples for Bioavailability / Bioequivalence

Not Applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (CV013011)

Procedure	Screening Visit (-18 for Part I Cohort 1 or -48 for Part II Cohort 2, up to 0 hours)	Pre-Randomization Procedures	Notes
Eligibility Assessments			
Informed Consent	X		
Review Inclusion/Exclusion Criteria	X	X	
Medical History	X		
Confirm administration of IV diuretic and time of administration	X		
Safety Assessments			
Complete Physical Examination	X		
Body Weight	X		
Height	X		
Vital Signs: Blood Pressure and Heart Rate	X	X*	Perform Semi-Recumbent (at a 30º angle). *Within 15 minutes prior to randomization
Respiratory Rate	X	X	
Use of Oxygen Supplementation, Oxygen Saturation	X	X	
Temperature	X	X*	*Within 15 minutes prior to randomization
Chest X-ray	X		As applicable, refer to section 3.3.1 X-ray obtained for the current episode of ADHF as part of standard of care may be used.

Table 5.1-1: Screening Procedural Outline (CV013011)

Procedure	Screening Visit (-18 for Part I Cohort 1 or -48 for Part II Cohort 2, up to 0 hours)	Pre-Randomization Procedures	Notes
12-Lead ECG (Electrocardiogram)	X		
Telemetry Monitoring		X	Begin within 2 hours prior to start of study medication infusion
Holter Monitoring (Part II Cohort 2 Only)		X	For participating sites. Begin within 2 hours prior to start of study medication infusion
Investigator Assessment of Congestion		X	Physical exam to assess signs and symptoms of congestion will include symptom assessments (dyspnea on exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea, persistent coughing or wheezing, fatigue, and abdominal discomfort), and signs assessment (peripheral edema, pulmonary rales, tachypnea and/or oxygen desaturation, increased jugular venous pressure, hepatomegaly, ascites).
Serious Adverse Events Assessment	X	X	Begins at time subject signs ICF
Review concomitant medications/procedures	X	X	
Local Laboratory Assessments			See Section 5.3.5.1 for Analytes
Hematology and Serum Chemistry	X		
eGFR	X		
Trough Serum Digoxin	X		If receiving digitalis glycosides
Hs Troponin T	X		
Coagulation Tests	X		Prothrombin Time (PT or PT-INR)
NT-proBNP or BNP	X		As per site preference

Table 5.1-1: Screening Procedural Outline (CV013011)

Procedure	Screening Visit (-18 for Part I Cohort 1 or -48 for Part II Cohort 2, up to 0 hours)	Pre-Randomization Procedures	Notes
Pregnancy Test	X		
Central Laboratory Assessments			See Section 5.3.5.2 for Analytes
Hematology and Serum Chemistry		X	
Hs Troponin T		X	
NT-proBNP, Serum Cystatin C, NGAL		X	
CRP		X	
Urinalysis		X	
Urine creatinine, Na+, and K+		X	
[redacted]			
Efficacy Assessments			
Resting Dyspnea measured by the Numerical Rating Scale (NRS)[a]		X	
Other Assessments			
Sensory Motor Survey		X	

[a] If subject is receiving supplemental oxygen, perform NRS without removing oxygen

Table 5.1-2: Treatment and In-Hospital Follow-up (CV013011)

Procedure	Hour 0-23[a] (Post Rand, Day 1)	Hour 24 ± 2	Hour 48 ± 2	Hour 72 ± 2	Hour 96 ± 2	Hour 120 ± 2 or Discharge [b c]	Notes (Time is relative to start of dosing)
Randomize Subject	X						Randomization must take place before Hour 0
Administer Study Medication	X						48 hour continuous infusion ***Study medication infusion begin promptly after randomization***
Safety Assessments							
Body Weight		X	X	X	X	X	
Vital Signs: Blood Pressure and Heart Rate[d]	X	X	X	X	X	X	Perform Semi-Recumbent (at a 30º angle) Day 1: Hours 0, 0.25 (15 min), 0.5 (30 min), 0.75 (45 min), 1, 1.5, 2, 4, **5***, 6, 8, **9***, 10, 12, 14, 16, 18, 20, 22 Hours: 24, 28, 32, 36, 40, 44 Hours 48, 54, 60, 66 Hour 72 Hour 96 Hour 120 Perform measurements before IV bag change, when possible. Repeats as per Section 5.3.1 Perform also if signs or symptoms of hypotension *Part I (Cohort 1) only
Respiratory Rate	X	X	X	X	X	X	Day 1: Hours 6 and 12
Use of Oxygen Supplementation,	X	X	X	X	X	X	Day 1: Hours 6 and 12

Table 5.1-2: Treatment and In-Hospital Follow-up (CV013011)

Procedure	Hour 0-23[a] (Post Rand, Day 1)	Hour 24 ± 2	Hour 48 ± 2	Hour 72 ± 2	Hour 96 ± 2	Hour 120 ± 2 or Discharge [b c]	Notes (Time is relative to start of dosing)
Oxygen Saturation							
Temperature		X	X	X	X	X	
12-Lead ECG		X	X	X		X	
Telemetry Monitoring	X						Continuous monitoring through Hour 50
Holter Monitoring (Part II Cohort 2 Only)	X						For participating sites. Continuous monitoring through Hour 52. 12-lead ECGs will be extracted at 3 timepoints prior to the start of the infusion and at the same timepoints as PK determinations up to and including 48 hours post-dose (See section 5.5) Subjects will be supinely resting in a semi-recumbent position for at least 10 minutes prior to and 5 minutes after each timepoint for ECG extraction (Day 1: Hour 0.75, 4*, 8*, 14, 48 and Hour 52). When ECG extractions coincide with 12-lead safety ECGs, blood draws and other assessments, ECG extractions should, when feasible, be performed in said order.
Investigator Assessment of Signs of Congestion		X	X	X	X	X	Physical exam to assess signs and symptoms of congestion will include symptom assessments (dyspnea on exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea,

Table 5.1-2: Treatment and In-Hospital Follow-up (CV013011)

Procedure	Hour 0-23[a] (Post Rand, Day 1)	Hour 24 ± 2	Hour 48 ± 2	Hour 72 ± 2	Hour 96 ± 2	Hour 120 ± 2 or Discharge [b c]	Notes (Time is relative to start of dosing)
							persistent coughing or wheezing, fatigue, and abdominal discomfort), and signs assessment (peripheral edema, pulmonary rales, tachypnea and/or oxygen desaturation, increased jugular venous pressure, hepatomegaly, ascites).
Assessment of Hypotension	X		X	X			Assessment of signs and symptoms of hypotension.
Serious Adverse Event Assessment	X						
Adverse Events Assessment	X						From Hour 0 to Hour 120. If subject is discharged before Hour 120, site asked to contact subject at Hour 120 for final AE collection
Concomitant Medications	X						
Local Laboratory Assessments							
Cumulative Urinary Output (Volume)		X	X	X	X	X	Provide daily volume
Pregnancy Test				X		X	WOCBP only
Central Laboratory Assessments							See Section 5.3.5.2 for Analytes
Hematology and Serum Chemistry		X	X	X		X	
Hs Troponin T		X	X	X		X	
NT-proBNP, Serum Cystatin C, NGAL		X	X	X		X	

Table 5.1-2: Treatment and In-Hospital Follow-up (CV013011)

Procedure	Hour 0-23[a] (Post Rand, Day 1)	Hour 24 ± 2	Hour 48 ± 2	Hour 72 ± 2	Hour 96 ± 2	Hour 120 ± 2 or Discharge [b c]	Notes (Time is relative to start of dosing)
CRP			X			X	
Urinalysis				X			
Urine creatinine, Na+ and K+		X	X	X		X	
Pharmacokinetics							See Section 5.5
Pharmacokinetic Blood Samples Collection and Preparation of Blood Samples	X		X	X			Part I Cohort 1: Day 1: Hour 0.75, 4, 8, 14 Hour 48 Hour 52 Part II Cohort 2: Day 1: Hour 0.75, 6, 14 Hour 48 Hour 52 Perform measurements before IV bag change or stopping the infusion, whenever possible. Collect sample when dose lowered due to a safety event and also at time of early discontinuation of study drug.
[redacted]							

Table 5.1-2: Treatment and In-Hospital Follow-up (CV013011)

Procedure	Hour 0-23[a] (Post Rand, Day 1)	Hour 24 ± 2	Hour 48 ± 2	Hour 72 ± 2	Hour 96 ± 2	Hour 120 ± 2 or Discharge [b c]	Notes (Time is relative to start of dosing)
Efficacy Assessments							
Resting Dyspnea measured by Numerical Rating Scale (NRS)[e]	X	X	X	X		X	Day 1: Hours 6 and 12
Resting Dyspnea measured by 7-point Likert Scale[e]	X	X	X	X		X	Day 1: Hours 6 and 12
Patient Global Assessment measured by 7-point Likert Scale[e]	X	X	X	X		X	Day 1: Hours 6 and 12
Assessments of Worsening Heart Failure		X	X	X	X	X	Documentation of Worsening Physical Signs and Symptoms of Heart Failure, and Documentation of Initiation or Increased dose of Parenteral Diuretic, Vasodilator and/or Inotropes, or Need for Mechanical interventions (mechanical ventilation, circulatory support, ultrafiltration or dialysis). Assessments to cover prior 24 hour period.
Wristworn Actigraphy monitoring device (watch) (Part II Cohort 2)			X	X	X	X	For participating sites. Provide the device to subjects at the end of the 48 hours infusion or when the study drug has been permanently discontinued
Other Assessments							
Sensory Motor Survey						X	

[a] Hour 0 defined as start of study medication infusion

[b] Visit to occur at Hour 120 ± 2 or Discharge, whichever comes first. If subject is discharged after Hour 120, no further protocol in-hospital visits are completed

[c] Assessments required at Discharge Visit should not be repeated if performed within previous 12 hours

[d] Vital signs should be taken within (± 0.25)

[e] If subject is receiving supplemental oxygen, perform NRS without removing oxygen

Table 5.1-3: Outpatient Follow-up (CV013011)

Procedure	Day 32 (± 2 Days) Clinic Visit[a]	Day 182 (± 5 Days) Phone Visit[b]	Notes
Safety Assessments			
Vital Signs: Blood Pressure and Heart Rate	X		When possible, perform Semi-Recumbent (at a 30º angle)
Respiratory Rate	X		
Body Weight	X		
Temperature	X		
Serious Adverse Events Assessment	X		
Local Laboratory Assessments			
Pregnancy Test	X		WOCBP only
Central Laboratory Assessments			See Section 5.3.5.2 for Analytes
Hematology and Serum Chemistry	X		
NT-proBNP, Serum Cystatin C, NGAL	X		
CRP	X		
Urinalysis	X		
Urine creatinine, Na+ and K+	X		
[redacted]			
Efficacy, Safety, and Other Assessments			
Healthcare Utilization Assessment	X		
Assessment of Mortality	X	X	
Sensory Motor Survey	X		

Table 5.1-3: Outpatient Follow-up (CV013011)

Procedure	Day 32 (± 2 Days) Clinic Visit[a]	Day 182 (± 5 Days) Phone Visit[b]	Notes
Actigraphy monitoring watch (Part II Cohort 2)	X		For participating sites. One time complete transfer of data from the actigraphy device to a dedicated website via an electronic docking station to occur during or immediately following the 32-days study visit

[a] Subjects in Japan who were enrolled after the end of global Part II enrollment will be followed for safety and rehospitalization endpoints through Day 32.

[b] Day 182 Phone Visit not applicable for Subjects in Japan who were enrolled after the end of global Part II enrollment, as they will be followed for safety and rehospitalization endpoints through Day 32 only.

5.1.1 Retesting During Screening or Lead-in Period

All screening laboratory will be performed locally, and tests may be repeated at the discretion of the Investigator as per site policy.

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

In an effort to find all possible well-qualified subjects, subjects that have discontinued the study as a screen failure (have not been randomized) are eligible for re-screening upon presentation for a subsequent episode of ADHF at the discretion of the Investigator.

If re-screened, the subject must be re-consented and a new subject number will be assigned by the IRT. Laboratory parameters and/or assessments that are included in Table 5.1-1, Screening Procedural Outline, must be repeated. The subject numbers and data will be linked in the clinical database.

5.1.2 Discharge

Discharge may occur as per institutions standard medical practice. It is recommended that subjects remain in the hospital for at least 24 hours after the completion of the 48-hour infusion of study drug for safety monitoring.

Subjects discharged prior to Hour 120 should complete the Hour 120/Discharge visit. Assessments required at the Hour 120/Discharge Visit as per Table 5.1-1 should not be repeated if performed within the previous 12 hours.

5.2 Study Materials

- 11-item Numerical Rating Scale
- 7-point to Likert Scale
- Sensory Motor Survey
- Pharmacy Manual
- Clinical Laboratory Manual
- Subject education materials and other site support tools

5.3 Safety Assessments

Additional procedures and assessments may be performed as a part of the subject's standard of care; however, data for these assessments will remain in the subject's medical record and is not be provided to BMS, unless needed to support an AE, SAE report, or as specifically requested by the Sponsor.

5.3.1 Assessment of Blood Pressure and Symptoms for Hypotension

The primary endpoint of the study is the incidence of clinically relevant hypotension, defined by SBP < 90 mm Hg (confirmed by a repeated value < 90 mm Hg) or symptoms of hypotension, up to 6 hours after the end of study drug infusion. Thus hypotension will be assessed by collection of symptoms and blood pressure measurements.

Symptomatic hypotension is defined as the presence of both low SBP and significant and/or non-resolving symptoms due to low blood pressure (eg, lightheadedness, dizziness, etc.).

Blood pressure measurements should be performed with the subject in a semi-recumbent (about a 30º angle) position, whenever possible.

Blood pressure will be measured as indicated in Table 5.1-2, within (± 5 min in the first hour then ± 0.25 (15 min)) of the specified time points. In addition, sites may perform measurements at intervals defined by institutional standard of care for subjects receiving vasodilators, but no less than what is described in Table 5.1-2.

If the study drug dose is modified (decreased, interrupted, resumed or discontinued) the frequency of blood pressure measurements will follow a more intensive schedule for up to 6 hours following the dose modification (Table 5.3.1-1). Upon completion of the intensive schedule, measurements can be either resumed per the original schedule, or follow the discontinuation schedule if the drug is permanently discontinued.

Table 5.3.1-1: Schedule of Intensive Blood Pressure Collection Following a Dose Modification

	30 minutes post	1 hour post	2 hours Post	4 hours post	6 hours post
Dose reduction	X	X	X	X	X
Dose interruption[a]	X	X	X	X	
Dose resumption[b]	X	X	X	X	X
Dose discontinuation	X	X	X	X	X[c]

[a] dose must be resumed within 4 hours of dose interruption. If interruption last beyond 4 hours, dose must be discontinued and discontinuation schedule must be followed.

[b] If dose is restarted within 4 hours following interruption, follow schedule for dose resumption

[c] After 6 hours, continue collecting blood pressure measurement at a minimum of every 12 hours through hour 72 or follow the local institutional standard of care protocol, whichever is more frequent.

In addition to assessments of blood pressure, the Investigator will be asked to collect and assess signs and symptoms of low blood pressure The details to be captured will include:

- Onset date/time
- Total duration of episode
- Lowest blood pressure during the episode

- Signs and symptoms associated with low blood pressure (such as confusion, dizziness, fatigue, auditory disturbances (such as tinnitus), lightheadedness, chest pain, visual disturbances, vomiting, syncope, etc)

Events of clinically relevant hypotension will also be recorded as an Adverse Event (see Section 6)
Management of study drug (interruption, discontinuation, re-start) is detailed in Section 4.5.1.
Hypotension endpoints are defined in Section 8.3.

5.3.2 Physical Measurements

Height: Measurement of height should be performed with the subject's shoes removed, if possible. The subject's knees should be straightened, head held erect, and eyes forward.

Weight: Measurement of weight should be performed with the subject having pockets empty, shoes removed, and bladder empty, when possible.

5.3.3 Physical Examination

A complete physical examination should include general appearance, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdomen, lymph nodes, extremities, neurological, skin, and musculoskeletal.

The individual performing the physical examinations must be licensed by state law (or applicable local law) to perform a physical examination.

5.3.4 Electrocardiogram

The Investigator should review and assess all ECGs for any clinically significant abnormalities, and initial and date the report.

The site should follow their standard practices for performing ECGs. Below is guidance to be used as a reference, if needed:

In preparation for the ECG, ensure there is minimal interference between the skin surface and the electrode. Use alcohol to prepare the skin at each electrode site. Thick chest hair should be shaved to ensure sufficient contact.

Before attaching electrodes to pick-up points, spread the electrode with electrode gel. Place the electrodes on bony areas, avoiding large muscle masses, to achieve better tracings as described below. The subject must be supine and should refrain from movement during the ECG recording.

Ensure that the subject and the electrodes (including the neutral electrode) are not exposed to conducting objects, even if grounded.

- RL: On the right leg (inside calf, midway between knee and ankle)
- LL: On the left leg (inside calf, midway between knee and ankle)
- RA: Right arm (on the inside)
- LA: Left arm (on the inside)
- V1: 4th intercostal space, at right sternal margin
- V2: 4th intercostal space, at left sternal margin

- V3: Midway between V2 and V4
- V4: 5th intercostal space at left midclavicular line
- V5: Same transverse level at V4, at anterior axillary line
- V6: Same transverse level at V4, at left midaxillary line

Keep one original ECG (print-out or electronic copy) in the medical chart and ensure a copy, assessed, initialed and dated by the Investigator, is maintained in the source documents for the study.

5.3.5 Laboratory Test Assessments

Subjects will have laboratory tests performed locally as necessary for treatment of ADHF following local practices. In addition, laboratory tests will be performed locally and centrally as described in the following sections.

5.3.5.1 Local Laboratory Assessments for Screening

The following local laboratory tests will be assessed as part of the screening evaluation. Local Laboratory results obtained for the current episode of heart failure as part of standard of care may be used. 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)
- Alkaline Phosphatase
- Total Bilirubin
- Blood Urea Nitrogen (BUN)
- Electrolytes
  - Sodium
  - Potassium
- Serum Creatinine (Scr)

Other Assessments
- eGFR, by locally used equation
- Trough Serum Digoxin (if receiving digitalis glycosides)
- Hs Troponin T (or other based on site's available assays)
- Coagulation Tests
  - Prothrombin Time (PT or PT-INR)

- NT-ProBNP or BNP (as per site preference)

5.3.5.2 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 in Section 5.

Hematology

- Hemoglobin
- Hematocrit
- White blood cell count and differential
- Erythrocytes (RBC)
- Erythrocyte mean corpuscular volume (MCV)*
- Erythrocyte mean corpuscular hemoglobin (MCH)*
- Erythrocyte mean corpuscular hemoglobin concentration (MCHC)*
- Platelet count
- Reticulocyte count*
  *performed at baseline, Hour 120 or Discharge, whichever comes first, and Day 32

Serum chemistry

- Aspartate Aminotransferase (AST, SGOT)
- Alanine Aminotransferase (ALT, SGPT)
- Alkaline Phosphatase
- Creatine Kinase (Creatine Phosphokinase) (CK) (CPK)
- Total Bilirubin
- Uric Acid
- Blood Urea Nitrogen (BUN)
- Electrolytes
  - Sodium
  - Potassium
  - Chloride
  - Bicarbonate
  - Glucose
  - Anion gap
  - Magnesium
- Total Protein
- Albumin
- Serum Creatinine (Scr)
- Calcium*
- Phosphorus*
  *performed at baseline, Hour 24, Hour 48 and Hour 120 or Discharge, whichever comes first.

Other Assessments
- eGFR, by MDRD
- Trough Serum Digoxin (if receiving digitalis glycosides)
- Hs Troponin T
- Coagulation Tests
  - Prothrombin Time (PT and PT-INR)
  - Partial thromboplastin time (PTT)
- NT-ProBNP
- Cystatin C
- CRP
- NGAL

Urinalysis
- pH, protein, glucose, leukocyte esterase, blood by dipstick
- Microalbumin
- Albumin: creatinine ratio
- Microscopy if dipstick positive for blood, leukocyte esterase or protein

The Central Laboratory and designated reference laboratories for this study will perform the analysis of all scheduled laboratory tests and will provide reference ranges for these tests. Urine dipstick testing for pregnancy (in WOCBP) at specified visits is to be done at the investigative site.

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.

5.3.6 Telemetry Monitoring

Telemetry monitoring will be performed to help monitor subject safety. The site will follow their normal operating procedures established for telemetry monitoring. Clinically significant findings from the telemetry monitoring will be recorded as AEs and SAEs per the Investigators decision.

5.3.7 Holter Recordings

Holter monitoring with extraction of serial ECGs will be performed in a sub-set of 51 patients in Part II Cohort 2 only, randomized 1:1:1 to placebo and the two active doses in Part II Cohort 2 of the study. The 12-lead Holter and ECG equipment will be supplied and supported by the sponsor and a core electrocardiographic laboratory. ECGs to be used in the analyses will be selected by pre-determined time points as defined in the Table of Assessments, and will be read centrally by a core electrocardiographic laboratory. The analysis will be described in detail in a separate analysis plan.

Ten 14-second digital 12-lead ECG tracings will be extracted from the continuous Holter recordings using the 'TQT Plus method', a computer-assisted and statistical process utilized by a core electrocardiographic laboratory.

At each protocol-specified timepoint, 10 ECG replicates will be extracted from a 5-minute "ECG window" (typically, the last 5 minutes of the 15-minute period when the subject is maintained in a supine or semi-recumbent quiet position. Subjects must be instructed to rest in a quiet position 15 minutes before each PK draw.

5.3.8 Imaging Assessment for the Study

Not Applicable.

5.4 Efficacy Assessments

5.4.1 Assessments of Worsening Heart Failure

The Investigator will be asked to indicate if a subject has experienced worsening heart failure, to document the signs, and symptoms that led to the assessment of worsening heart failure, and to document the intensification of treatment implemented for worsening heart failure. Assessment is to be done once daily covering the prior 24-hour period as per the scheduled times in Table 5.1-2.

In this trial, worsening heart failure is defined as **new or worsening signs and/or symptoms of heart failure that require**:

- **Intensification of IV therapy** for heart failure (such as initiation, restart or up-titration of IV diuretics, IV nitrates or other IV vasoactive drugs), *and/or*
- Addition of a mechanical support, either:
  - Ventilatory (mechanical ventilation, noninvasive ventilation),
  - Circulatory (Intra-Aortic Balloon Pump (IABP), ventricular assist device) or
  - Use of ultrafiltration, hemofiltration or hemodialysis specifically for the management of WHF

The presence of WHF must be documented by the investigator recording the signs, symptoms, and/or laboratory assessments that led the conclusion that the subject had worsened.

Symptoms of heart failure may include: dyspnea on exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea, persistent coughing or wheezing, fatigue, and abdominal discomfort.

Signs of heart failure might include: pulmonary rales, tachypnea and/or oxygen desaturation, increased jugular venous pressure, hepatomegaly, peripheral edema, an increase in body weight, oliguria, and signs of hypo-perfusion such as mental confusion, hypotension, and cool skin

5.4.2 Investigator Assessment of Signs of Congestion

The Investigator will be asked to assess the subject's signs of congestion using the following criteria:

1) Bilateral peripheral edema using a 4-point scale
   a) 0 absent
   b) 1+ Trace (Barely perceptible indent, skin rebounds quickly)

c) 2+ Feet and ankles (Easily identifiable indent, skin rebounds in 15-30 sec, edema limited to feet and ankles)

d) 3+ Lower legs or thighs (Easily identifiable indent, skin rebounds in > 30 sec, edema extended to lower legs or thighs)

2) Bilateral pulmonary rales: Auscultation of the lungs applying a 3-point scale
   a) 0 absent
   b) 1+ < 1/3 up lung fields,
   c) 2+ ≥ 1/3 up lung fields
3) Jugular venous distension (absent / present)
4) Hepatic enlargement (absent / present)
5) Orthopnea: The subject should be observed after being in the lowest recumbent position for 10-15 minutes
   a) Absent – subject has no sensation of dyspnea in recumbent position
   b) Present - dyspnea develops in the recumbent position and is relieved by elevation of the head with pillows
6) Ascites
   a) Absent
   b) Present

5.4.3 Physical activity monitoring using a wrist-worn actigraphy device (watch)

Physical activity will be measured in a subset of approximately 100 patients in Part II of the trial only, using an actigraphy wearable device worn on the wrist (wristwatch) that utilizes an accelerometer to monitor the occurrence and degree of motion[47].

All sites participating in the accelerometry sub-study will provide the device to subjects at the end of the 48 hours infusion or when the study drug has been permanently discontinued. Study participants accepting to participate in the sub-study will wear the device continuously during 30 days follow-up period, with the exception of the charging period (battery life expected to be approximately 10-12 days), via a charger provided to the patient. Data collected by the device will be uploaded during the 32-days study visit via an electronic docking station at the site.

5.5 Pharmacokinetic Assessments

Blood samples will be collected for pharmacokinetic assessments as described in Table 5.5-1.

Table 5.5-1: Pharmacokinetic Assessments

Time Relative to Dosing Hour (window)	Time (Relative to Dosing) Hour: Min	PK Blood Sample
0.75 (± 0.25)	00:45	X
4 (± 0.5)	04:00	X
8 (± 0.5)	8:00	X
14 (± 4)	14:00	X
48 (± 1)	48:00	X
52 (± 1)	52:00	X
Dose lowered due to safety event (± 0.5)	Misc.	X
Early Discontinuation	Misc.	X

Collect the 4 and 8 hour PK samples immediately prior to the IV bag change whenever possible. In addition, collect a PK sample from the subject 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.

[redacted]

5.7 Outcomes Research Assessments

5.7.1 Dyspnea Assessments

The sensation of dyspnea is subjective, but dyspnea relief is important to subjects and has been long quantified in clinical trials using patient-reported outcome scales that have previously been used to assess the efficacy of other interventions in ADHF subjects.

In this trial, subjects are asked to report their absolute current severity of dyspnea on an 11-point numerical rating scale (NRS; range 0 to 10) and their current level of dyspnea relative to baseline using 7-level Likert scales.

5.7.1.1 Dyspnea Numerical Rating Scale

The numerical rating scale (NRS) will be used to assess the degree of dyspnea (breathlessness), measured using an 11-point scale provided by the Sponsor.

5.7.1.2 Dyspnea Likert Scale

Subject will be presented with the following question: "We would like to measure how you think your breathing is. Please circle the number next to the description that best indicates how you are breathing right now, compared to when you first started the study drug."

3 = Markedly better

2 = Moderately better

1 = Minimally better

0 = No change

-1 = Minimally worse

-2 = Moderately worse

-3 = Markedly worse

5.7.2 Healthcare Utilization

Following discharge from the index hospitalization, the occurrence of rehospitalizations and emergency department visits for heart failure and other causes of cardiovascular disease will be documented. Rehosptalizations will include subjects who are either under observation or admitted as an inpatient with a length of stay ≥ 24 hours. Emergency department visits will include urgent, unplanned visits in a monitored healthcare setting with a length of stay < 24 hours. Only emergency department visits that do not result in a hospitalization will be counted as separate healthcare encounters.

In the event that the subject reports rehospitalizations or emergency department visits through Day 32 after the index hospitalization, the reason for the rehospitalization/ED visit will be recorded and, where possible, will be confirmed with the hospital or the subject's physician. The investigator should make every effort to obtain a discharge summary. If the subject is currently hospitalized and unable to attend the visit, then the investigator should make every effort to reschedule the visit when medically appropriate and to obtain the discharge summary when available.

The primary reason for the rehospitalization/ED visit will be categorized by the investigator into 1 of the following categories:

- Heart failure related event involves a primary diagnosis of HF, where the subject has new or worsening symptoms, objective evidence of new or worsening HF, and receives new or intensification of treatment including an IV diuretic
- Other cardiovascular, non-heart failure related event involves a primary diagnosis of cardiovascular disease other than HF including MI, resuscitate sudden cardiac death or other cardiovascular cause (eg, stroke)
- Non-cardiovascular event involves primary diagnoses other than HF and CV disease

5.7.3 Mortality

Investigators will follow all subjects in global part II to Day 182 for mortality. Subjects in Japan who were enrolled after the end of global Part II enrollment will be followed through Day 32.

Investigators will be asked to report deaths and categorize them as either cardiovascular or non-cardiovascular death. All deaths will be assumed to be cardiovascular unless a non-cardiovascular cause can be clearly provided. Below is guidance for Investigator classification:

Cardiovascular Death:

Cardiovascular death includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes

Non-cardiovascular Death:

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

5.8 Other Assessments

5.8.1 Sensory Motor Survey

Subject will be complete a 5 question interview relating to presence and degree of specified characteristics relating to sensory and motor function, with responses indicating either none, mild, moderate, or severe felt over the past 24 hours.

5.9 Additional Research Collection

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

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

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

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

- Residual plasma and serum samples from exploratory biomarker collections (see Table 5.6-1 and Table 5.9-1) will be retained for additional research purposes
- Samples will be securely stored by the BMS Biorepository in Hopewell, NJ or at a BMS approved third party storage management facility
- Samples will be stored in a coded fashion; and no researcher will have access to the key, which is securely held at the clinical site, so that there is no direct ability for a researcher to connect a sample to a specific individual
- Additional research samples will be retained for 15 years or the maximum allowed by applicable law. No additional sampling is required for residual collections

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

Table 5.9-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Time points for which residual samples will be retained
Plasma exploratory biomarker	All
Serum exploratory biomarker	All
Urine	All

6 ADVERSE EVENTS

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

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

Related: There is a reasonable causal relationship between study drug administration and the AE.

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

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

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

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

6.1 Serious Adverse Events

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

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

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

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

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

Worsening heart failure, including hospital readmission is considered an SAE and should be reported as such.

NOTE:

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

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

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing.

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

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

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

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

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

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

All SAEs must be followed to resolution or stabilization.

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

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug and continue through Hour 120.

AEs will be collected from Hour 0 to Hour 120. If a subject is discharged prior to Hour 120, the site is asked to follow-up with the subject at Hour 120 to complete AE collection.

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

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

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE eCRF 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 subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy

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

6.4 Pregnancy

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

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

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

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

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

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

6.5 Overdose

Include any project specific definition of overdose in addition to the following mandatory statement as the last sentence:

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. All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details).

6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

AND No other immediately apparent possible causes of aminotransaminases (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

Given the short treatment course, baseline liver enzyme testing will be performed at Pre-randomization and post-treatment liver enzyme testing will be performed at Hour 120 and Day 32.

All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

7.1 Data Monitoring Committee

An independent DMC will review safety data to ensure subjects safety. The full role of the DMC will be defined in the DMC charter. The DMC will review unblinded accumulating data on a regular basis and make recommendations to BMS and the Executive Committee regarding subjects currently enrolled and yet to be enrolled in the trial. The DMC may recommend suspension of enrolment or early termination of the trial, for safety reasons. See Section 8.5 for additional information.

The DMC will consider available endpoint information, in addition to safety events, before making any study stopping recommendations to the Executive Committee and Sponsor, as per guidelines set forth in the DMC charter.

7.2 Executive Committee

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 interim and final analyses with Sponsor.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

For Part I (Cohort 1), approximately 50 subjects per group will be randomized to placebo or an incremental dose of BMS-986231 (3 - 6 - 12 μg/kg/min). Under a sample decision rule (eg, observed doubling with more than a 4% difference) and assuming clinically relevant hypotension incidences of 5% or 10% in the placebo group, the posterior probabilities of detecting an increase of 4-fold or 3-fold in incidence, respectively, are 86% and 80%, respectively. If there is no increase in clinically relevant hypotension, then the posterior probabilities of falsely detecting an increase are 11-12%.

For Part II (Cohort 2), approximately 70 subjects per group will be randomized to placebo or one of the two active dose levels of BMS-986231. Under a sample decision rule (eg, observed 1.8-fold increase with more than a 3% difference) and assuming clinically relevant hypotension incidences of 5% or 10% in the placebo group, the posterior probabilities of detecting an increase of 3-fold or 2.5-fold in incidence, respectively, are 82% and 80%, respectively. If there is no increase in clinically relevant hypotension, then the posterior probabilities of falsely detecting an increase are 13-15%. These probabilities do not reflect multiple comparison.

While the enrollment in the main study protocol will continue until 210 patients have been randomized globally in Part II (Cohort 2), enrollment may continue further only in Japan until approximately 18 total Japanese subjects are randomized

With regards to overall performance for selection of a maximally tolerated dose, a sample size of 50 per group for Part I (Cohort 1), along with 70 per group for Part II (Cohort 2) will identify a maximally tolerated dose approximately 50-70%, based on detecting an increase of 3-fold or 2.5-fold in incidence, and using sample decision rules that are consistent with above. Also, the design will provide an option to select a titrated 12 μg/kg/min dose approximately 60% of the time when that dose is tolerated, but a non-titrated 12 μg/kg/min dose is not tolerated. Conversely, the study design will not identify a maximally tolerated dose from Part II (Cohort 2) approximately 80%-85% of the time when no maximally tolerated dose exists

8.2 Populations for Analyses

- The Enrolled Subjects Data Set will consist of all subjects who sign informed consent
- The Randomized Subjects Data Set will consist of all randomized subjects who have started study drug infusion. This is also known as the Intent to Treat (ITT) population. Data in this data set will be analyzed based on randomized treatment group
- The Treated Subjects Data Set will consist of all subjects who receive any study drug infusion. This will be the primary safety data set. Data in this data set will be analyzed based on randomized treatment, except in the following cases:
    - If a subject received the same incorrect treatment throughout the 48 hours study drug infusion or until discontinuation of the study drug, then the subject will be analyzed based on the treatment received

- If a subject received study drug from more than one treatment group, and none of the administrations were consistent with the assigned randomized treatment group, then the subject will be analyzed based on the first treatment received

- The Pharmacokinetic analysis dataset will consist of all subjects who receive BMS-986231 and have at least one post dose PK sample

8.3 Endpoints

8.3.1 Primary Endpoint

The primary endpoint is the incidence of clinically relevant hypotension, defined by SBP < 90 mm Hg (confirmed by a repeated value < 90 mm Hg) or symptoms of hypotension, up to 6 hours after the end of study drug infusion.

8.3.2 Secondary Endpoints

- Change in NT-proBNP from baseline to Hour 24, 48, 72, 120 or discharge (whichever comes first), and at Day 32
- Change in patient-reported resting dyspnea from baseline through Hour 72, as measured by the area under the curve (AUC) of the 11-point Numerical Rating Scale (NRS) obtained at baseline, and Hours 6, 12, 24, 48, and 72

8.3.4 Safety Endpoints.

Safety endpoints consist of the following:

- The incidence of symptomatic hypotension up to 6 hours after the end of study drug infusion
- The incidence of SBP < 90 mm Hg (confirmed by a repeated value)
- Change in Troponin T from baseline to Hour 24, 48, and 72
- Percentage of subjects who have died (all- cause and CV related)

Additionally, the percentage of subjects with discontinuation due to symptomatic hypotension, as well as percentage of subjects with down-titrations, interruptions or discontinuations as a result of low blood pressure, either protocol specified clinically relevant hypotension, or asymptomatic decreases will be assessed. Other safety endpoints include the incidence of Adverse Events and Marked Laboratory Abnormalities, changes from baseline in vital signs, ECGs, physical measurements and laboratory assessments through Hour 120 or discharge, whichever comes first. The incidence of Serious Adverse Events will be assessed though Day 32.

8.4 Analyses

Results from Part I (Cohort 1) and Part II (Cohort 2) will be presented separately.

Subjects in Japan who started treatment after last patient randomization date of subjects who were enrolled before closure of the 210 subject global enrollment will not be part of the main global part II Day 32 interim analysis or the main global part II Day 182 analysis. Details will be provided in the statistical analysis plan

For analyses involving baseline, the baseline value is defined by the last value prior to the start of infusion, unless otherwise noted.

8.4.1 Demographics and Baseline Characteristics

Frequency distributions and summary statistics for demographic and baseline variables will be presented by treatment group and for all subjects combined. Demographic variables to be summarized include: age, gender, race, and geographic region.

Baseline variables to be summarized include physical measurements (height, body weight, body mass index), vital signs (systolic blood pressure, diastolic blood pressure, and heart rate), disease characteristics (New York Heart Association Class prior to admission, ejection fraction, heart failure etiology, number of heart failure hospitalizations in past year, time since original HF diagnosis and since first diuretic use in the current episode of decompensation to first treatment, commorbities, including history of coronary artery disease, hypertension, or diabetes, and presence of atrial fibrillation), important laboratory variables (including NT-proBNP, serum sodium and eGFR), and current heart failure medications.

8.4.2 Primary, Secondary, and Exploratory Endpoints Analyses

8.4.2.1 Primary Endpoint Analysis

The incidence of clinically relevant hypotension from the start to 6 hours after the end of study drug infusion will be summarized by treatment. Point estimates and 95% CIs for event rates will be presented by treatment, together with point estimates and 95% CIs for the risk difference and relative risk between each BMS-986231 arm and placebo.

8.4.2.2 Secondary Endpoint Analyses

NT-proBNP will be summarized descriptively by treatment for each time point, as well as change from baseline.

Analyses for changes from baseline in the resting dyspnea as measured by the 11-point NRS will be done using a longitudinal repeated measures model, with baseline value and region as covariates. A trapezoidal rule will be applied to calculate AUC using model-estimated values from the time points. Missing values for the dyspnea NRS will not be imputed, except if a NRS cannot be obtained because the subject has died or is physically unable to complete the form. In these cases, a worst score imputation will be used for that time point.

[redacted]

8.4.3 Safety Analyses

Troponin T will be summarized descriptively by treatment for each time point, as well as change from baseline.

Percentage of subjects who have died (all- cause and CV related) will be summarized descriptively by treatment.

All recorded adverse events 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.

Percentage of subjects with discontinuations due to symptomatic hypotension, as well as percentage of subjects with down-titrations or interruptions or discontinuations as a result of hypotension, either protocol specified clinically relevant hypotension, or asymptomatic decreases will be summarized descriptively by treatment.

In addition, the final infusion dose at the completion of 48 hours infusion will be summarized descriptively by treatment. The subjects who discontinued prematurely from infusion would be counted as having a final infusion dose of 0 μg/kg/min.

8.4.4 Pharmacokinetic Analyses

Blood samples will be collected from all subjects at 0.75, 4, 8, 14, and 48 hours during infusion and 4 hours after end of infusion and plasma concentrations will be measured using LC-MS. 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.

[redacted]

8.4.6 Outcomes Research Analyses

Healthcare utilization is defined as the percentage of subjects with rehospitalizations and emergency department visits will be summarized descriptively by treatment group for HF or other cardiovascular disease separately.

8.4.7 Other Analyses

Not applicable.

8.5 Interim Analyses

Two interim analyses will be performed for this study. An interim analysis will be performed following the completion of the last visit at Hour 120 in Part I (Cohort 1). The analysis will include data for all Cohort 1 subjects through at least Hour 120. The DMC, Executive Committee and representatives from the Sponsor will assess hypotension, as well as additional safety information, in addition to any available endpoint events. The outcome will determine whether 12 μg/kg/min is a sufficiently tolerated dose to be used in Part II (Cohort 2). The dose selection decision for Part II will be made by the Sponsor in collaboration with the Executive Committee, with input from the DMC. The doses for Part II (Cohort 2) will be determined based on general guiding principles and considered in the context of the totality of the data. For example, some of the critical information that will be considered evaluating the suitability 12 μg/kg/min for Part II will include the percentage of subjects completing the 48 hour infusion, percentage of subjects with temporary interruptions or permanent discontinuation of study drug, percentage of subjects with clinically relevant hypotension, percentage of subjects with symptomatic hypotension, and other key safety endpoints of interest (eg, renal function).

The second interim analysis will be performed when 210 randomized subjects reach the last visit at Day 32 in Part II (Cohort 2) in order to facilitate drug development decisions. The study analysis team will then provide top-line results to the project team.

After each DMC review, the Sponsor will be advised by the DMC Chair as to whether the study is safe to proceed as written, that the study should be modified, or that the study should be stopped. In addition to these periodic reviews, the DMC will review the unblinded data from Part I in parallel with the review by the executive committee and the Sponsor. A similar recommendation will be provided to the Sponsor, that the study is to proceed as written, or should be modified or stopped.

Analyses will consist of summaries of the available data. No formal inferences requiring any adjustment to statistical significance level will be performed

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects. If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s), the deviation or change will be submitted as soon as possible to:

- IRB/IEC

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

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority, must be sent to BMS. If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

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

9.1.2 Monitoring

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

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

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

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

9.1.2.1 Source Documentation

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

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

9.2 Records

9.2.1 Records Retention

The investigator (or head of 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 or designee 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.

9.2.2 Study Drug Records

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

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

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

9.2.3 Case Report Forms

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

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

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

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

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

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

9.3 Clinical Study Report and Publications

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

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

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee

- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

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

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraception's must be discussed in the event that the subject chooses to forego complete abstinence.
Presentation	First dose of IV diuretic for the current episode

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ADHF	acute decompensated heart failure
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	Aminotransaminases
AUC	area under the concentration-time curve
BiPAP	bilevel positive airway pressure
BMS	Bristol-Myers Squibb
BNP	brain natriuretic peptide
BP	blood pressure
bpm	Beats per minute
BUN	blood urea nitrogen
C	Celsius
CCU	coronary care unit
CFR	Code of Federal Regulations
CI	cardiac index
CPAP	continuous positive airway pressure
CRF	Case Report Form, paper or electronic
CVA	cerebral vascular accident
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Emergency Department
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
ESR	Expedited Safety Report
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
H	Hour
HF	heart failure

Term	Definition
HFrEF	heart failure with reduced ejection fraction
HNO	Nitroxyl
HRT	hormone replacement therapy
Hs	high sensitivity
IABP	Intra-Aortic Balloon Pump
ICH	International Conference on Harmonisation
ICU	intensive care unit
Ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous
K3EDTA	potassium ethylenediaminetetraacetic acid
Kg	Kilogram
LVEF	left ventricular ejection fraction
mg	Milligram
min	Minute
Mm Hg	millimeters of mercury
MS	mass spectrometry
MUGA	multigated acquisition
µg	Microgram
Na+	Sodium
NIMP	non-investigational medicinal products
NO	nitric oxide
NRS	numerical rating scale
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
PADP	Pulmonary Artery Diastolic Pressure
PC	peripheral capillary wedge pressure
PDE3	phosphodiesterase 3

Term	Definition
PDE5	phosphodiesterase type 5
PK	pharmacokinetics
PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cell
SAE	serious adverse event
TIA	transient ischemic attack
WOCBP	women of childbearing potential

APPENDIX 1 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

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

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

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

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

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

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

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

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

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

UNACCEPTABLE METHODS OF CONTRACEPTION

A. Periodic abstinence (calendar, symptothermal, post-ovulation methods)
B. Withdrawal (coitus interruptus)
C. Spermicide only
D. Lactation amenorrhea method (LAM)
E. Periodic abstinence (calendar, symptothermal, post-ovulation methods)
F. Withdrawal (coitus interruptus)
G. Spermicide only
H. Lactation amenorrhea method (LAM)
I. Progestogen only hormonal contraception associated with inhibition of ovulation or where inhibition of ovulation is not the primary mode of action
J. Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®
K. Intrauterine hormone-releasing system (IUS)
L. Diaphragm with spermicide
M. Cervical cap with spermicide
N. Vaginal sponge with spermicide
O. Male or female condom with or without spermicide*

[redacted]

APPENDIX 2 CORE AND EXTENDED ADME GENE LIST

Core ADME Gene List:

Gene Symbol	Full Gene Name	Class
ABCB1	ATP-binding cassette, sub-family B (MDR/TAP), member 1	Transporter
ABCC2	ATP-binding cassette, sub-family C (CFTR/MRP), member 2	Transporter
ABCG2	ATP-binding cassette, sub-family G (WHITE), member 2	Transporter
CYP1A1	cytochrome P450, family 1, subfamily A, polypeptide 1	Phase I
CYP1A2	cytochrome P450, family 1, subfamily A, polypeptide 2	Phase I
CYP2A6	cytochrome P450, family 2, subfamily A, polypeptide 6	Phase I
CYP2B6	cytochrome P450, family 2, subfamily B, polypeptide 6	Phase I
CYP2C19	cytochrome P450, family 2, subfamily C, polypeptide 19	Phase I
CYP2C8	cytochrome P450, family 2, subfamily C, polypeptide 8	Phase I
CYP2C9	cytochrome P450, family 2, subfamily C, polypeptide 9	Phase I
CYP2D6	cytochrome P450, family 2, subfamily D, polypeptide 6	Phase I
CYP2E1	cytochrome P450, family 2, subfamily E, polypeptide 1	Phase I
CYP3A4	cytochrome P450, family 3, subfamily A, polypeptide 4	Phase I
CYP3A5	cytochrome P450, family 3, subfamily A, polypeptide 5	Phase I
DPYD	dihydropyrimidine dehydrogenase	Phase I
GSTM1	glutathione S-transferase M1	Phase II
GSTP1	glutathione S-transferase pi	Phase II
GSTT1	glutathione S-transferase theta 1	Phase II
NAT1	N-acetyltransferase 1 (arylamine N-acetyltransferase)	Phase II
NAT2	N-acetyltransferase 2 (arylamine N-acetyltransferase)	Phase II
SLC15A2	solute carrier family 15 (H+/peptide transporter), member 2	Transporter
SLC22A1	solute carrier family 22 (organic cation transporter), member 1	Transporter
SLC22A2	solute carrier family 22 (organic cation transporter), member 2	Transporter
SLC22A6	solute carrier family 22 (organic anion transporter), member 6	Transporter
SLCO1B1	solute carrier organic anion transporter family, member 1B1	Transporter
SLCO1B3	solute carrier organic anion transporter family, member 1B3	Transporter
SULT1A1	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 1	Phase II
TPMT	thiopurine S-methyltransferase,	Phase II
UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1	Phase II
UGT2B15	UDP glucuronosyltransferase 2 family, polypeptide B15	Phase II
UGT2B17	UDP glucuronosyltransferase 2 family, polypeptide B17	Phase II
UGT2B7	UDP glucuronosyltransferase 2 family, polypeptide B7	Phase II

Extended ADME Gene List:

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

Gene Symbol	Full Gene Name	Class
GSTT2	glutathione S-transferase theta 2	Phase II
SLC10A1	solute carrier family 10 (sodium/bile acid cotransporter family), member 1	Transporter
SLC15A1	solute carrier family 15 (oligopeptide transporter), member 1	Transporter
SLC22A11	solute carrier family 22 (organic anion/cation transporter), member 11	Transporter
SLC22A8	solute carrier family 22 (organic anion transporter), member 8	Transporter
SLC7A5	solute carrier family 7 (cationic amino acid transporter, y+ system), member 5	Transporter
SLCO1A2	solute carrier organic anion transporter family, member 1A2	Transporter
SLCO2B1	solute carrier organic anion transporter family, member 2B1	Transporter
SULT1A2	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 2	Phase II
SULT1A3	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 3	Phase II
SULT1B1	sulfotransferase family, cytosolic, 1B, member 1	Phase II
UGT1A3	UDP glucuronosyltransferase 1 family, polypeptide A3	Phase II
UGT1A6	UDP glucuronosyltransferase 1 family, polypeptide A6	Phase II
UGT1A7	UDP glucuronosyltransferase 1 family, polypeptide A7	Phase II
UGT1A8	UDP glucuronosyltransferase 1 family, polypeptide A8	Phase II
UGT1A9	UDP glucuronosyltransferase 1 family, polypeptide A9	Phase II
UGT2A1	UDP glucuronosyltransferase 2 family, polypeptide A1	Phase II
UGT2B11	UDP glucuronosyltransferase 2 family, polypeptide B11	Phase II
UGT2B28	UDP glucuronosyltransferase 2 family, polypeptide B28	Phase II
UGT2B4	UDP glucuronosyltransferase 2 family, polypeptide B4	Phase II
ABCA1	ATP-binding cassette, sub-family A (ABC1), member 1	Transporter
ABCA4	ATP-binding cassette, sub-family A (ABC1), member 4	Transporter
ABCB11	ATP-binding cassette, sub-family B (MDR/TAP), member 11	Transporter

Gene Symbol	Full Gene Name	Class
ABCB4	ATP-binding cassette, sub-family B (MDR/TAP), member 4	Transporter
ABCB5	ATP-binding cassette, sub-family B (MDR/TAP), member 5	Transporter
ABCB6	ATP-binding cassette, sub-family B (MDR/TAP), member 6	Transporter
ABCB7	ATP-binding cassette, sub-family B (MDR/TAP), member 7	Transporter
ABCC1	ATP-binding cassette, sub-family C (CFTR/MRP), member 1	Transporter
ABCC10	ATP-binding cassette, sub-family C (CFTR/MRP), member 10	Transporter
ABCC11	ATP-binding cassette, sub-family C (CFTR/MRP), member 11	Transporter
ABCC5	ATP-binding cassette, sub-family C (CFTR/MRP), member 5	Transporter
ABCC6	ATP-binding cassette, sub-family C (CFTR/MRP), member 6	Transporter
ABCC8	ATP-binding cassette, sub-family C (CFTR/MRP), member 8	Transporter
ABCC9	ATP-binding cassette, sub-family C (CFTR/MRP), member 9	Transporter
ABCG1	ATP-binding cassette, sub-family G (WHITE), member 1	Transporter
ADH1A	alcohol dehydrogenase 1A (class I), alpha polypeptide	Phase I
ADH1B	alcohol dehydrogenase IB (class I), beta polypeptide	Phase I
ADH1C	alcohol dehydrogenase 1C (class I), gamma polypeptide	Phase I
ADH4	alcohol dehydrogenase 4 (class II), pi polypeptide	Phase I
ADH5	alcohol dehydrogenase 5 (class III), chi polypeptide,methionyl aminopeptidase 1	Phase I
ADH6	alcohol dehydrogenase 6 (class V)	Phase I
ADH7	alcohol dehydrogenase 7 (class IV), mu or sigma polypeptide	Phase I
ALDH1A1	aldehyde dehydrogenase 1 family, member A1	Phase I
ALDH1A2	aldehyde dehydrogenase 1 family, member A2	Phase I
ALDH1A3	aldehyde dehydrogenase 1 family, member A3	Phase I
ALDH1B1	aldehyde dehydrogenase 1 family, member B1	Phase I

Gene Symbol	Full Gene Name	Class
ALDH2	aldehyde dehydrogenase 2 family (mitochondrial)	Phase I
ALDH3A1	aldehyde dehydrogenase 3 family, memberA1	Phase I
ALDH3A2	aldehyde dehydrogenase 3 family, member A2	Phase I
ALDH3B1	aldehyde dehydrogenase 3 family, member B1	Phase I
ALDH3B2	aldehyde dehydrogenase 3 family, member B2	Phase I
ALDH7A1	aldehyde dehydrogenase 7 family, member A1	Phase I
ALDH8A1	aldehyde dehydrogenase 8 family, member A1	Phase I
ALDH9A1	aldehyde dehydrogenase 9 family, member A1	Phase I
AOX1	aldehyde oxidase 1	Phase I
ARNT	aryl hydrocarbon receptor nuclear translocator	Modifier
CBR1	carbonyl reductase 1	Phase I
CBR3	carbonyl reductase 3	Phase I
CDA	cytidine deaminase	Modifier
CYB5R3	cytochrome b5 reductase 3	Phase I
CYP11A1	cytochrome P450, family 11, subfamily A, polypeptide 1	Phase I
CYP11B1	cytochrome P450, family 11, subfamily B, polypeptide 1	Phase I
CYP11B2	cytochrome P450, family 11, subfamily B, polypeptide 2	Phase I
CYP17A1	cytochrome P450, family 17, subfamily A, polypeptide 1	Phase I
CYP1B1	cytochrome P450, family 1, subfamily B, polypeptide 1	Phase I
CYP20A1	cytochrome P450, family 20, subfamily A, polypeptide 1	Phase I
CYP20A1	cytochrome P450, family 20, subfamily A, polypeptide 1	Phase I
CYP21A2	cytochrome P450, family 21, subfamily A, polypeptide 2	Phase I
CYP24A1	cytochrome P450, family 24, subfamily A, polypeptide 1	Phase I

Gene Symbol	Full Gene Name	Class
CYP26A1	cytochrome P450, family 26, subfamily A, polypeptide 1	Phase I
CYP27A1	cytochrome P450, family 27, subfamily A, polypeptide 1	Phase I
CYP2A13	cytochrome P450, family 2, subfamily A, polypeptide 13	Phase I
CYP2A7	cytochrome P450, family 2, subfamily A, polypeptide 7	Phase I
CYP2C18	cytochrome P450, family 2, subfamily C, polypeptide 18	Phase I
CYP2F1	cytochrome P450, family 2, subfamily F, polypeptide 1	Phase I
CYP2J2	cytochrome P450, family 2, subfamily J, polypeptide 2	Phase I
CYP39A1	cytochrome P450, family 39, subfamily A, polypeptide 1	Phase I
CYP3A43	cytochrome P450, family 3, subfamily A, polypeptide 43	Phase I
CYP3A7	cytochrome P450, family 3, subfamily A, polypeptide 7	Phase I
CYP4B1	cytochrome P450, family 4, subfamily B, polypeptide 1	Phase I
CYP4F11	cytochrome P450, family 4, subfamily F, polypeptide 11	Phase I
CYP51A1	cytochrome P450, family 51, subfamily A, polypeptide 1	Phase I
EPHX2	epoxide hydrolase 2, cytoplasmic	Phase I
FMO1	flavin containing monooxygenase 1	Phase I
FMO2	flavin containing monooxygenase 2	Phase I
FMO4	flavin containing monooxygenase 4	Phase I
FMO5	flavin containing monooxygenase 5	Phase I
GPX2	glutathione peroxidase 2 (gastrointestinal)	Phase I
GPX3	glutathione peroxidase 3 (plasma)	Phase I
GPX7	glutathione peroxidase 7	Phase I
GSR	glutathione reductase	Phase I
GSTK1	glutathione S-transferase kappa 1	Phase II

Gene Symbol	Full Gene Name	Class
GSTM5	glutathione S-transferase M5	Phase II
GSTZ1	glutathione transferase zeta 1 (maleylacetoacetate isomerase)	Phase II
NNMT	nicotinamide N-methyltransferase	Phase II
NR1I2	nuclear receptor subfamily 1, group I, member 2	Modifier
NR1I3	nuclear receptor subfamily 1, group I, member 3	Modifier
PNMT	phenylethanolamine N-methyltransferase	Phase II
PON1	paraoxonase 1	Phase I
PON2	paraoxonase 2	Phase I
PON3	paraoxonase 3	Phase I
POR	P450 (cytochrome) oxidoreductase	Modifier
PPARD	peroxisome proliferative activated receptor, delta	Modifier
PPARG	peroxisome proliferative activated receptor, gamma	Modifier
RXRA	retinoid X receptor, alpha	Modifier
SLC10A2	solute carrier family 10 (sodium/bile acid cotransporter family), member 2	Transporter
SLC13A1	solute carrier family 13 (sodium/sulfate symporters), member 1	Transporter
SLC13A2	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 2	Transporter
SLC13A3	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 3	Transporter
SLC16A1	solute carrier family 16 (monocarboxylic acid Transporter), member 1	Transporter
SLC19A1	solute carrier family 19 (folate transporter), member 1	Transporter
SLC22A10	solute carrier family 22 (organic anion/cation transporter), member 10	Transporter
SLC22A12	solute carrier family 22 (organic anion/cation transporter), member 12	Transporter
SLC22A13	solute carrier family 22 (organic cation transporter), member 13	Transporter
SLC22A14	solute carrier family 22 (organic cation transporter), member 14	Transporter

Gene Symbol	Full Gene Name	Class
SLC22A15	solute carrier family 22 (organic cation transporter), member 15	Transporter
SLC22A16	solute carrier family 22 (organic cation transporter), member 16	Transporter
SLC22A17	solute carrier family 22 (organic cation transporter), member 17	Transporter
SLC22A18	solute carrier family 22 (organic cation transporter), member 18	Transporter
SLC22A18AS	solute carrier family 22 (organic cation transporter), member 18 antisense	Transporter
SLC22A3	solute carrier family 22 (extraneuronal monoamine transporter), member 3	Transporter
SLC22A4	solute carrier family 22 (organic cation transporter), member 4	Transporter
SLC22A5	solute carrier family 22 (organic cation transporter), member 5	Transporter
SLC22A7	solute carrier family 22 (organic anion transporter), member 7	Transporter
SLC22A9	solute carrier family 22 (organic anion/cation transporter), member 9	Transporter
SLC27A1	solute carrier family 27 (fatty acid transporter), member 1	Transporter
SLC28A1	solute carrier family 28 (sodium-coupled nucleoside transporter), member 1	Transporter
SLC28A2	solute carrier family 28 (sodium-coupled nucleoside transporter), member 2	Transporter
SLC28A3	solute carrier family 28 (sodium-coupled nucleoside transporter), member 3	Transporter
SLC29A1	solute carrier family 29 (nucleoside Transporter), member 1	Transporter
SLC29A2	solute carrier family 29 (nucleoside Transporter), member 2	Transporter
SLC2A4	solute carrier family 2 (facilitated glucose transporter), member 4	Transporter
SLC2A5	solute carrier family 2 (facilitated glucose/fructose transporter), member 5	Transporter
SLC5A6	solute carrier family 5 (sodium-dependent vitamin transporter)	Transporter
SLC6A6	solute carrier family 6 (neurotransmitter transporter, taurine), member 6	Transporter
SLC7A8	solute carrier family 7 (cationic amino acid transporter, y+ system), member 8	Transporter
SLCO1C1	solute carrier organic anion transporter family, member 1C1	Transporter
SLCO2A1	solute carrier organic anion transporter family, member 2A1	Transporter

Gene Symbol	Full Gene Name	Class
SLCO3A1	solute carrier organic anion transporter family, member 3A1	Transporter
SLCO4A1	solute carrier organic anion transporter family, member 4A1	Transporter
SLCO4C1	solute carrier organic anion transporter family, member 4C1	Transporter
SLCO5A1	solute carrier organic anion transporter family, member 5A1	Transporter
SLCO6A1	solute carrier organic anion transporter family, member 6A1	Transporter
SULT1C1	sulfotransferase family, cytosolic, 1C, member 1	Phase II
SULT1C2	sulfotransferase family, cytosolic, 1C, member 2	Phase II
SULT1E1	sulfotransferase family 1E, estrogen-preferring, member 1	Phase II
SULT2A1	sulfotransferase family, cytosolic, 2A, DHEA preferring, member 1	Phase II
SULT2B1	sulfotransferase family, cytosolic, 2B, member 1	Phase II
TAP1	transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	Transporter
UGT1A10	UDP glucuronosyltransferase 1 family, polypeptide A10	Phase II
UGT1A4	UDP glucuronosyltransferase 1 family, polypeptide A4	Phase II
UGT1A5	UDP glucuronosyltransferase 1 family, polypeptide A5	Phase II
UGT2B10	UDP glucuronosyltransferase 2 family, polypeptide B10	Phase II
ABCC13	ATP-binding cassette, sub-family C (CFTR/MRP), member 13	Transporter
ARSA	arylsulfatase A	Modifier
CAT	catalase	Modifier
CHST8	carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 8	Phase II
CYP19A1	cytochrome P450, family 19, subfamily A, polypeptide 1	Phase I
CYP26C1	cytochrome P450, family 26, subfamily C, polypeptide 1	Phase I
CYP27B1	cytochrome P450, family 27, subfamily B, polypeptide 1	Phase I
CYP2R1	cytochrome P450, family 2, subfamily R, polypeptide 1	Phase I

Gene Symbol	Full Gene Name	Class
CYP2S1	cytochrome P450, family 2, subfamily S, polypeptide 1	Phase I
CYP46A1	cytochrome P450, family 46, subfamily A, polypeptide 1	Phase I
CYP4A11	cytochrome P450, family 4, subfamily A, polypeptide 11	Phase I
CYP4F12	cytochrome P450, family 4, subfamily F, polypeptide 12	Phase I
CYP4F2	cytochrome P450, family 4, subfamily F, polypeptide 2	Phase I
CYP4F3	cytochrome P450, family 4, subfamily F, polypeptide 3	Phase I
CYP4F8	cytochrome P450, family 4, subfamily F, polypeptide 8	Phase I
CYP4Z1	cytochrome P450, family 4, subfamily Z, polypeptide 1	Phase I
CYP7B1	cytochrome P450, family 7, subfamily B, polypeptide 1	Phase I
CYP8B1	cytochrome P450, family 8, subfamily B, polypeptide 1	Phase I
DHRS13	dehydrogenase/reductase (SDR family) member 13	Phase I
DHRS2	dehydrogenase/reductase (SDR family) member 2	Phase I
GPX1	glutathione peroxidase 1	Phase I
GPX4	glutathione peroxidase 4 (phospholipid hydroperoxidase)	Phase I
GPX5	glutathione peroxidase 5 (epididymal androgen-related protein)	Phase I
GPX6	glutathione peroxidase 6 (olfactory)	Phase I
GSS	glutathione synthetase	Phase I
GSTCD	glutathione S-transferase, C-terminal domain containing	Phase II
HNF4A	hepatocyte nuclear factor 4, alpha	Modifier
HNMT	histamine N-methyltransferase	Phase II
HSD11B1	hydroxysteroid (17-beta) dehydrogenase 11	Phase I
HSD17B11	hydroxysteroid (17-beta) dehydrogenase 11	Phase I
HSD17B14	hydroxysteroid (17-beta) dehydrogenase 14	Phase I

Gene Symbol	Full Gene Name	Class
LOC731356	similar to dehydrogenase/reductase (SDR family) member 4 like 2	Phase I
MGST1	microsomal glutathione S-transferase 1	Phase II
MGST2	microsomal glutathione S-transferase 2	Phase II
MGST3	microsomal glutathione S-transferase 3	Phase II
MPO	myeloperoxidase	Modifier
NOS1	nitric oxide synthase 1 (neuronal)	Phase I
NOS2A	nitric oxide synthase 2A (inducible, hepatocytes)	Phase I
NOS3	nitric oxide synthase 3 (endothelial cell)	Phase I
PPARA	peroxisome proliferator-activated receptor alpha	Modifier
SERPINA7	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 7	Modifier
SLC7A7	solute carrier family 7 (cationic amino acid transporter, y+ system), member 7	Transporter
SOD1	superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	Modifier
SOD2	superoxide dismutase 2, mitochondrial	Modifier
SOD3	superoxide dismutase 3, extracellular precursor	Modifier
SULF1	sulfatase 1	Phase I
SULT4A1	sulfotransferase family 4A, member 1	Phase II
TAP2	transporter 2, ATP-binding cassette, sub-family B (MDR/TAP)	Transporter
UGT8	UDP glycosyltransferase 8 (UDP-galactose ceramide galactosyltransferase)	Phase II
XDH	xanthine dehydrogenase	Phase I
ADHFE1	alcohol dehydrogenase, iron containing, 1	Phase I
CHST1	carbohydrate (keratan sulfate Gal-6) sulfotransferase 1	Phase II
CHST10	carbohydrate sulfotransferase 10	Phase II
CHST11	carbohydrate (chondroitin 4) sulfotransferase 11	Phase II

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

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

APPENDIX 3 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 02b, 30-May-2019

The below changes are due to a DMC recommendation to increase oversight of patients at the initiation of the infusion.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02B		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 5.1-2: Treatment and In-Hospital Follow-up (CV013011)	Additional Blood Pressure and Heart Rate Measurements at: 15 minutes, 45 minutes, and 1.5 hours.	[redacted]
Section 5.3.1: Assessment of Blood Pressure and Symptoms for Hypotension	Clarification that blood pressure measurements within ± 5 min in the first hour, then ± 15 min of the specified timepoints in Table 5.1-2.	

Overall Rationale for the Revised Protocol 02a, 13-Mar-2019

These changes serve to clarify the milestone, timing of enrollment and inclusion/exclusion criteria of the Japanese population. While the enrollment in the main study protocol will continue until 210 patients have been randomized globally in Part II (Cohort 2), enrollment in Japan may continue further only in Japan until approximately 18 total Japanese subjects are randomized.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02A		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.1: Study Design and Duration; Synopsis	Section modified to add: while the enrollment in the main study protocol will continue until 210 patients have been randomized globally in Part II (Cohort 2), enrollment in Japan may continue further only in Japan until approximately 18 total Japanese subjects are randomized.	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02A		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.3.1: Inclusion Criteria; Synopsis	Inclusion criteria # 2G) was modified to decrease the minimum allowable BNP levels from ≥ 400 pg/mL (116 pmol/L) to ≥ 350 pg/mL (101 pmol/L) and NT-proBNP levels from ≥ 1600 pg/mL (189 pmol/L) to ≥ 1400 pg/mL (166 pmol/L)	[redacted]
Section 3.3.1: Inclusion Criteria; Synopsis	Inclusion criteria # 2H) was modified to decrease the minimum allowable body weight from ≥ 50 kg to ≥ 40 kg	
Section 3.3.2: Exclusion Criteria; Synopsis	Exclusion Criteria # 4D) was modified to: Subjects treated with oral phosphodiesterase type 5 (PDE5) inhibitor sildenafil, vardenafil or avanafil within 24 hours of screening or treated with tadalafil within 4 days of screening, oral inotropic agents (eg, pimobendan) or oral vasopressin V2 receptor antagonist (eg, tolvaptan) initiated for the current ADHF episode. NOTE: chronic use of tolvaptan is not exclusionary.	
Section 4.6.2 Other Blinding and Unblinding	Section was modified to include: The second interim analysis will be performed when 210 randomized subjects reach the last visit at Day 32 in Part II (Cohort 2). The study analysis team will then provide top-line results to the project team.	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02A		
Section Number & Title	**Description of Change**	**Brief Rationale**
	The follow-up to Day 182 for both Part I and Part II will be site-and-subject blinded. Japanese subjects enrolled as part of the 210 subject global cohort (Part II, Cohort 2) will be site-and-subject blinded until the end of the study in Japan.	
Section 8.1: Sample Size Determination	Section was modified to add: While the enrollment in the main study protocol will continue until 210 patients have been randomized globally in Part II (Cohort 2), enrollment may continue further only in Japan until approximately 18 total Japanese subjects are randomized	[redacted]
Section 8.4: Analyses	Section was modified to add: Subjects in Japan who started treatment after last patient randomization date of subjects who were enrolled before closure of the 210 subject global enrollment will not be part of the main global Part II Day 32 interim analysis. Details will be provided in the statistical analysis plan	
Section 8.5: Interim Analyses	Section was modified to add: The second interim analysis will be performed when 210 randomized subjects reach the last visit at Day 32 in Part II (Cohort 2) in order to facilitate drug development decisions. The study analysis team will then provide	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02A		
Section Number & Title	**Description of Change**	**Brief Rationale**
	top-line results to the project team. An additional interim analysis may be performed following completion of the last visit at Day 32 of the last enrolled Japanese subject.	

Overall Rationale for the Revised Protocol 02, 09-Apr-2018

These changes serve to clarify procedures for Part II Cohort 2 of the study. Part I Cohort 1 of the study is not impacted. Changes include:

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	[redacted]
Section 3.3.2 Exclusion Criteria	Exclusion criteria # 2b was modified to clarify: Suspected acute lung disease (eg, pneumonia or asthma) or severe chronic lung disease (eg, severe chronic obstructive pulmonary disease, pulmonary fibrosis, patients with hypercapnia or requiring home oxygen therapy or chronic oral steroids.)	
[redacted]		

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 3.1 Study Design and Duration	Changed to: Study Medication infusion must start within 18 hours of presentation (or 48 hours in Part II Cohort 2 of the trial), with presentation defined as the first dose of diuretic for current episode	[redacted]
Section 5.1.2 Treatment and In-Hospital Follow-up	Addition of window to collect vital signs within .25 hours of specified time points.	
All	Minor formatting and typographical corrections	