Official Title of Study:

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

NCT Number: NCT03016325

Document Date (Date in which document was last revised): June 21, 2017

STATISTICAL ANALYSIS PLAN
FOR

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

PROTOCOL(S) CV013011

VERSION # 1

TABLE OF CONTENTS

LIST OF TABLES

[redacted]

2 STUDY DESCRIPTION

2.1 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.

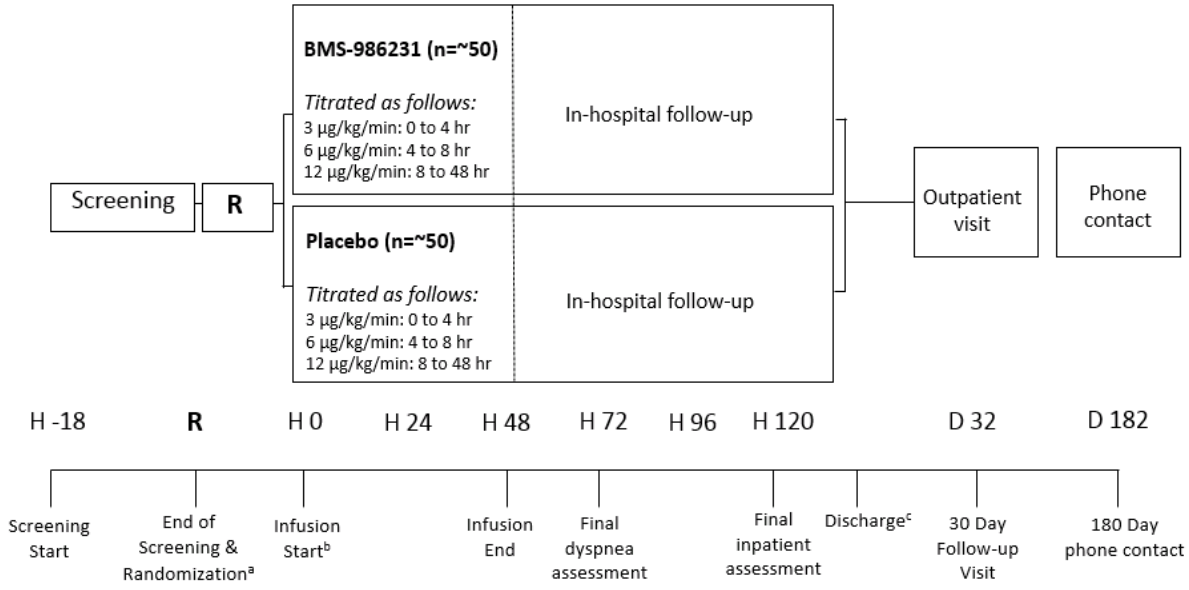
Subjects that are randomized in Part I of the study will not be allowed to participate in Part II.

In Part I (Cohort 1) of the study, approximately 100 subjects will be randomized in a 1:1 ratio to 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.

The study design schematic is presented in Figure 2.1-1 for Part I (Cohort 1) and Figure 2.1-2 for Part II (Cohort 2).

Figure 2.1-1: Study Design Schematic Part I (Cohort 1)

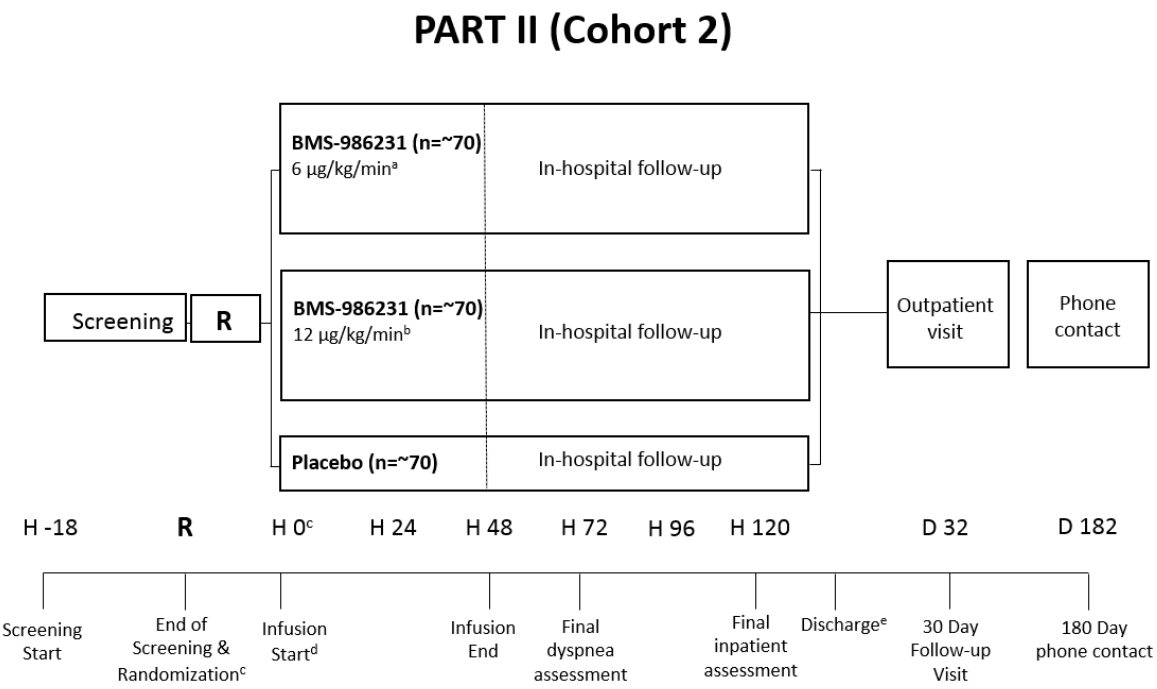


[a] Every effort should be made to initiate study drug administration promptly after randomization

[b] Study Medication infusion must start within 18 hours of presentation, 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 2.1-2: 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, 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, 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 inpatient assessment at Hour 120 or discharge. 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 Day 182 follow-up visit, or withdrawal date (for subjects who withdraw prematurely from the study) by any patient, whichever comes later.

2.2 Treatment Assignment

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 meets 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 the following regions: North America, Europe, and Latin America (Argentina only).

2.3 Blinding and Unblinding

The Data Monitoring Committee (DMC; see Section 2.5.1) 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 (see section 7.11).

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 2.5) 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.

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 pharmacokinetics (PK) and safety data, as needed. These summaries will not reveal individual subjects' treatment assignments.

2.4 Protocol Amendments

This statistical analysis plan (SAP) is based on the revised protocol version 01 which incorporates Amendment 01, dated 11-Oct-2016.

2.5 Data Monitoring Committee and Other External Committees

2.5.1 Data Monitoring Committee

An independent DMC will review safety data to ensure safety of subjects in the trial. The full role of the DMC will be defined in a separate 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 7.11 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.

2.5.2 Executive Committees

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.

3 OBJECTIVES

3.1 Primary

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)

3.2 Secondary

Secondary objectives include the following:

- 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)

3.3 Safety

Safety objectives include the following:

- Evaluate the effect of BMS-986231 on the incidence of symptomatic hypotension
- Evaluate the effect 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

[redacted]

4 ENDPOINTS

4.1 Efficacy Endpoints

4.1.1 Primary Efficacy Endpoint

There is no primary efficacy endpoint. The primary safety endpoint is discussed in Section 4.2.1.

4.1.2 Secondary Efficacy Endpoints

Secondary endpoints include the following:

- 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

4.2 Safety Endpoints

4.2.1 Primary Safety Endpoint

The primary safety endpoint is the incidence of clinically relevant hypotension, defined by SBP < 90 mm Hg (confirmed by a repeated value < 90 mm Hg, see Section 8.1) or symptoms of hypotension, up to 6 hours after the end of study drug infusion.

4.2.2 Other Safety Endpoints

Other safety endpoints include 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, see Section 8.1) up to 6 hours after the end of study drug infusion
- Change in Troponin T from baseline to Hour 24, 48, and 72
- Percentage of subjects who have died (all- cause and CV(cardiovascular) 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.

[redacted]

5 SAMPLE SIZE AND POWER

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 is established from Part II (Cohort 2) approximately 80%-85% of the time when no maximally tolerated dose exists.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

Screening period starts from 18 hours prior to start of study drug infusion to Hour 0 (the start of study drug infusion). In-hospital follow-up starts from the end of study drug infusion to Hour 120 or discharge, whichever comes first. Day 32 follow-up occurs 32 days after the start of study drug infusion. Day 182 follow-up occurs 182 days after the start of study drug infusion.

Please see the study design (Section 2.1) for the details on study periods.

6.2 Treatment Regimens

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

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.

See Pharmacy Manual for additional dosing information.

6.3 Populations for Analyses

The following populations will be used for the 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 (PK Population) will consist of all subjects who receive BMS-986231 and have at least one post dose PK sample. Additionally, the Evaluable PK Population is defined as subjects who have adequate PK profiles.

7 STATISTICAL ANALYSES

SAS® version 9.2 or higher will be used for statistical analyses, tabulations and graphical presentations. S-Plus® may be also used for graphical presentations.

7.1 General Methods

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

Except as noted otherwise, descriptive summaries will be presented for continuous variables using number of subjects (N), mean, standard deviation (SD), median, minimum and maximum. Descriptive summaries for categorical variables will utilize counts and percentages. Several analyses noted in subsequent sections will present 95% confidence intervals (CIs), but no pre-specified significance testing will be included.

Adverse events and medical history will be coded according to the most recent Medical Dictionary for Regulatory Activities (MedDRA) version. Previous and concomitant medications will be coded using the WHO Drug Dictionary.

7.2 Study Conduct

Protocol deviations identified as significant will be captured in a trial management system and reported in the CSR. Relevant protocol deviations are those that are programmable and could potentially affect the interpretability of the study results. The following protocol deviations will be defined as relevant protocol deviations and listed:

- Error in treatment assignment resulting in a subject being dosed with an incorrect treatment
- Subject not treated within 24 hours of first dose of intravenous diuretic (the time difference between start of infusion and first dose of intravenous diuretic > 24 hours)
- Systolic blood pressure (SBP) < 105 mm Hg at screening or Hour 0
- Violation of inclusion criterion 2 (b): Subjects not hospitalized for ADHF
- Violation of inclusion criterion 2 (g): Not having 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
- Violation of inclusion criterion 2 (h): Have no elevated NT-proBNP ≥ 1600 pg/mL (516 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 subjects with atrial fibrillation: no NT-proBNP ≥ 2400 pg/ml or BNP ≥ 600 pg/ml

- Violation of exclusion criterion 4 (a): Subjects administered IV or transdermal nitrate therapy prior to randomization, when at least one of the following criteria are not 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
- Violation of exclusion criterion 4 (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 prior to the start of screening
- Initiation of PDE5 inhibitors during study drug infusion

7.3 Study Population

7.3.1 Subject Disposition

Subject disposition will be listed. Summary tables reflecting the number of subjects who are enrolled, who are randomized, and reasons for not being randomized, will be presented as overall.

The number of subjects who do not complete the treatment of 48 hours infusion, both overall and according to reasons for discontinuation from the treatment, will be summarized for all treated subjects, as overall and by treatment. Subjects who have temporary interruption or down-titration of study drug but do not discontinue permanently will be treated as completing the treatment. The number of subjects who do not complete the study phase, both overall and according to reasons for not completing, will be summarized for all treated subjects, as overall and by treatment. Summary tables will be presented for study phases ending at Hour 120 (or discharge, whichever comes first), Day 32, and Day 182.

7.3.2 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 for all treated subjects. Demographic variables to be summarized include: age, gender, race, and geographic region. See Table 7.3-1 for countries in each region.

Table 7.3-1: Demographics and Baseline Characteristics

Region	Country
North America	Canada and United States
Europe	Czech Republic, France, Germany, Greece, Italy, Netherlands, Poland, Spain, and United Kingdom
Latin America	Argentina

Baseline variables to be summarized include the following:

- 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 (as collected in the CRF Hear Failure Etiology page at screening)
  - Number of heart failure hospitalizations in past year
  - Time since original HF diagnosis to first treatment of study drug
  - Time since first diuretic use in the current episode of decompensation to first treatment of study drug
  - Comorbidities listed in "Specific Disease History" CRF page, including but not limited to coronary artery disease, hypertension, diabetes, and presence of atrial fibrillation
- Important laboratory variables (including NT-proBNP, serum sodium and eGFR)
- Current heart failure medications

Start time of first diuretic use will be obtained from "Previous and Concomitant Intravenous Medications" CRF page.

Current heart failure medications will be taken from CRF previous and concomitant IV and non-IV medications pages with Use of "Heart Failure" and start date prior to first treatment of study drug. The CRF pages collect IV medications administered starting from one week prior to randomization.

7.3.3 Physical Measurements

Physical measurements such as body weight and height will be summarized by nominal visit for all treated subjects, as overall and by treatment. Measurements will also be listed for all treated subjects.

7.3.4 Medical History and Previous Medications

Medical history and previous medications taken prior to dosing will be listed for all treated subjects.

7.4 Extent of Exposure

Study drug administration and randomization schedule will be documented as per subject listings.

Any non-study medications taken by subjects, any conducted non-study medical treatment procedures, and any utilized non-study diagnostic procedures will also be listed.

Percentage of subjects with discontinuation due to symptomatic hypotension, as well as percentage of subjects with down-titrations or discontinuations as a result of low blood pressure, either protocol specified clinically relevant hypotension, or asymptomatic decreases will be analyzed and presented in the same manner as the primary endpoint.

The final infusion dose at the completion of 48 hours infusion will be summarized descriptively by treatment. The subjects who discontinue prematurely from infusion will be counted as having a final infusion dose of 0 µg/kg/min. Subjects who are down-titrated and complete the 48 hours infusion will be counted as having a final infusion dose of 1/2 of the scheduled dose at time of down-titration. For example, the final dose will be 3 µg/kg/min if down-titration occurs when 6 µg/kg/min is administered for a subject in Part I (Cohort 1) and the subject otherwise complete dosing after the down-titration.

7.5 Efficacy

7.5.1 Primary Efficacy Analysis

There is no primary efficacy analysis for this study. The primary safety analysis is discussed in Section 7.6.1.

7.5.2 Secondary Efficacy Analysis

NT-proBNP will be summarized descriptively for all treated subjects by treatment for each time point, as well as change from baseline. Geometric mean and coefficient of variation (%CV) will also be presented for the original values and percent of baseline.

The NRS is an ordinal scale of 0 to 10. A score of 0 represents “I am not breathless at all” and 10 represents “I am the most breathless I can possibly imagine”.

To incorporate the correlations among NRS assessments at different time points and an appropriate representation of effect of baseline assessments, the change from baseline at time point *t* (Hour 24, 48, and 72) in NRS assessments will be analyzed using a longitudinal repeated measures method. The model will include treatment, region and time as fixed effects and baseline value as covariate. Furthermore, interaction terms of time by treatment, time by region and time by baseline value will be included. An unstructured variance-covariance matrix for the NRS assessments within same subject will be used (Autoregressive structure will be used if the model does not converge with unstructured matrix.). The SAS® procedure PROC MIXED will be used.

After obtaining the estimates of mean change from baseline at time point *t* in NRS assessments, the mean change in AUC within a treatment group or difference in mean change in AUC between treatment groups will be estimated within the framework of the mixed model, using the formula based on the Trapezoidal rule:

$$\Delta AUC = \sum_{i=1}^{3} (t_{i+1} - t_i) \frac{y_{t_{i+1}} + y_{t_i}}{2}$$

where y_{t_i} is the estimate of mean change from baseline at target time t_i in a treatment group for estimation of mean change in AUC within treatment group, and for estimation of difference in change in AUC between treatment groups, y_{t_i} is the estimate of mean difference between treatment groups in change from baseline at target time t_i . The variability of ΔAUC will also be estimated

within the framework of the mixed model in SAS using variability from terms used in the ESTIMATE statement.

Missing values for the dyspnea NRS will only be imputed 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 (i.e. 10) imputation will be used for that time point. Missing values for subjects who are discharged prior to Hour 120 will not be imputed.

7.6 Safety

All safety presentations will be based on the Treated Subject Data Set.

7.6.1 Primary Safety 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% confidence interval (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. The confidence intervals will be calculated using an exact method. The 95% confidence intervals for the relative risk and risk difference will be obtained using an exact procedure that inverted the 2-sided test statistics (Agresti and Min, 2001)[1].

The event rate is calculated as the number of subjects experiencing at least one clinically relevant hypotension from the start to 6 hours after the end of study drug infusion, divided by the total number of subjects receiving study treatment.

The incidence of symptomatic hypotension up to 6 hours after the end of study drug infusion, as well as the incidence of SBP < 90 mm Hg (confirmed by a repeated measure) will be analyzed and presented in the same manner as the primary endpoint.

7.6.2 Other Safety Analyses

7.6.2.1 Deaths

All reported deaths after a subject is enrolled (i.e., has signed the informed consent) will be listed separately by subject.

Percentage of subjects who have died (all- cause and CV related) through Day 32 and Day 182, and percentage of subjects who have heart failure hospitalizations or CV mortality through Day 32 will be analyzed and presented in the same manner as the primary endpoint, respectively.

7.6.2.2 Serious Adverse Events

All reported serious adverse events (SAEs) will be listed by System Organ Class (SOCs) and Preferred Terms (PTs) for all enrolled subjects. SAEs with onset time from the start of study treatment, up to and including 32 days after the start of study treatment will be included in the summary tables. SAEs will be coded and grouped into PT by SOC (see section 7.6.2.3).

7.6.2.3 Adverse Events

All AEs will be coded and grouped into PT by SOC, using current version of Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be summarized and listed by SOCs and PTs.

Non-serious AEs with onset time from the start of study treatment, up to and including 120 hours after the start of study treatment will be included in the summary tables. Events will be assigned to the study treatment administered to the subject. The proportion of subjects having an adverse event will be calculated as the number of subjects experiencing the event, divided by the total number of subjects receiving study treatment.

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

Where a subject has the same adverse event, based on preferred terminology, reported multiple times in a single analysis period, the subject will only be counted once at the preferred terminology level in adverse event frequency tables.

Where a subject has multiple adverse events within the same system organ class in a single analysis period, the subject will only be counted once at the system organ class level in adverse event frequency tables.

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

- Relationship to study medication
- Intensity of event
- Onset date and time

When reporting adverse events by intensity, in addition to providing a summary table based on the event selection criteria detailed above, summary tables will also be provided based on the most intense event during the analysis period - independent of relationship to study medication. For these tables, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- Intensity of event
- Onset date and time

Subjects will only be counted once in the 'Total' at their maximum intensity, regardless of SOC or PT.

7.6.2.4 Clinical Laboratory Evaluations

The results of all protocol-specified clinical laboratory tests will be listed. Scheduled laboratory measurements and corresponding change from baseline values will be summarized by treatment and scheduled time points for each laboratory test.

The criteria used for classifying laboratory test results as markedly abnormal will be listed.

Laboratory results for subjects with any marked laboratory abnormality (scheduled and unscheduled) will be listed. This listing will include all observations for the specific laboratory test and subject, not only the marked laboratory abnormalities. The frequency of subjects with any marked laboratory abnormality as well as hematology, serum chemistry, and urinalysis marked abnormalities, based on pre-specified criteria (see Table 7.6.2.4-1), will be presented.

Troponin T will be summarized descriptively by treatment for each time point, as well as change from baseline. Geometric mean and coefficient of variation (%CV) will also be presented for the original values and percent of baseline.

Table 7.6.2.4-1: Laboratory MA Criteria

Parameter	Test Code	Direction of Change	MA Criteria in US Standard Units (apply to labs collected after baseline only)	MA Criteria in SI Units (apply to labs collected after baseline only)
HEMATOLOGY				
Hemoglobin	HB	Low only	> 2 g/dl decrease compared to pre-dose or Value ≤ 8 g/dl	> 20 g/l decrease compared to pre-dose or Value ≤ 80 g/l
Hematocrit	HCT	Low only	< 0.75 × pre-dose	< 0.75 × pre-dose
Erythrocytes	RBC	Low only	< 0.75 × pre-dose	< 0.75 × pre-dose
Platelet Count	PLAT	Low Only	< 100,000/mm^3 (or < 100× 10^9 cells/L)	< 100× 10^9 cells/L
Leukocytes	WBC	Low/High	< 0.75 × LLN or > 1.25 × ULN, or if pre-dose < LLN then use < 0.8 × pre-dose or > ULN if pre-dose > ULN then use > 1.2 × pre-dose or < LLN	< 0.75 × LLN or > 1.25 × ULN, or if pre-dose < LLN then use < 0.8 × pre-dose or > ULN if pre-dose > ULN then use > 1.2 × pre-dose or < LLN
Neutrophils (absolute)	NEUTA	Low Only	< 1.0 × 10^3 cells/μL	< 1.0 ×10^9 cells/L
LIVER/KIDNEY				
Alkaline Phosphatase	ALP	High only	> 2 × ULN	> 2 × ULN
Aspartate Aminotransferase	AST	High only	> 3 × ULN, > 5 × ULN, > 10 × ULN	> 3 × ULN, > 5 × ULN, > 10 × ULN
Alanine Aminotransferase	ALT	High only	> 3 × ULN, > 5 × ULN, > 10 × ULN	> 3 × ULN, > 5 × ULN, > 10 × ULN
Bilirubin, Total	TBILI	High only	> 2 × ULN	> 2 × ULN

Table 7.6.2.4-1: Laboratory MA Criteria

Parameter	Test Code	Direction of Change	MA Criteria in US Standard Units (apply to labs collected after baseline only)	MA Criteria in SI Units (apply to labs collected after baseline only)
Blood Urea Nitrogen	BUN	High only	>2 × ULN	>2 × ULN
ELECTROLYTES				
Sodium, Serum	NA	Low/High	< 0.95 × LLN or > 1.05× ULN, or if pre-dose < LLN then use < 0.95 × pre-dose or >ULN if pre-dose > ULN then use > 1.05 × pre-dose or < LLN	< 0.95 × LLN or > 1.05× ULN, or if pre-dose < LLN then use < 0.95 × pre-dose or >ULN if pre-dose > ULN then use > 1.05 × pre-dose or < LLN
Potassium, Serum	K	Low/High	< 0.9× LLN or > 1.1× ULN, or if pre-dose < LLN then use < 0.9 × pre-dose or > ULN if pre-dose > ULN then use > 1.1 × pre-dose or < LLN	< 0.9× LLN or > 1.1× ULN, or if pre-dose < LLN then use < 0.9 × pre-dose or > ULN if pre-dose > ULN then use > 1.1 × pre-dose or < LLN
Chloride, Serum	CL	Low/High	< 0.9 × LLN OR > 1.1 × ULN, or if pre-dose < LLN then use < 0.9 × pre-dose or > ULN if pre-dose > ULN then use > 1.1 × pre-dose or < LLN	< 0.9 × LLN OR > 1.1 × ULN, or if pre-dose < LLN then use < 0.9 × pre-dose or > ULN if pre-dose > ULN then use > 1.1 × pre-dose or < LLN
Calcium, Total	CA	Low/High	< 0.8 × LLN or > 1.2 × ULN, or if pre-dose < LLN then use < 0.75 × pre-dose or > ULN if pre-dose > ULN then use > 1.25 × pre-dose or < LLN	< 0.8 × LLN or > 1.2 × ULN, or if pre-dose < LLN then use < 0.75 × pre-dose or > ULN if pre-dose > ULN then use > 1.25 × pre-dose or < LLN
Bicarbonate	HCO3	Low/High	< 0.75 × LLN or > 1.25 × ULN, or if pre-dose < LLN then use < 0.75 × pre-dose or > ULN if pre-dose > ULN then use > 1.25 × pre-dose or < LLN	< 0.75 × LLN or > 1.25 × ULN, or if pre-dose < LLN then use < 0.75 × pre-dose or > ULN if pre-dose > ULN then use > 1.25 × pre-dose or < LLN
OTHER CHEMISTRY				
Creatine Kinase	CK	High only	> 5 × ULN	> 5 × ULN
Total Protein	TPRO	Low/High	< 0.9 × LLN or > 1.1 × ULN, or if pre-dose < LLN then use 0.9 × pre-dose or > ULN if pre-dose > ULN then use 1.1 × pre-dose or < LLN	< 0.9 × LLN or > 1.1 × ULN, or if pre-dose < LLN then use 0.9 × pre-dose or > ULN if pre-dose > ULN then use 1.1 × pre-dose or < LLN

Table 7.6.2.4-1: Laboratory MA Criteria

Parameter	Test Code	Direction of Change	MA Criteria in US Standard Units (apply to labs collected after baseline only)	MA Criteria in SI Units (apply to labs collected after baseline only)
Glucose, Serum Fasting	GLUCF	Low/High	< 0.8 × LLN or > 1.5 × ULN, or if pre-dose < LLN then use < 0.8 × pre-dose or > ULN if pre-dose > ULN then use > 2.0 × pre-dose or <LLN	< 0.8 × LLN or > 1.5 × ULN, or if pre-dose < LLN then use < 0.8 × pre-dose or > ULN if pre-dose > ULN then use > 2.0 × pre-dose or <LLN
Uric Acid	URIC	High only	> 1.5 × ULN, or if pre-dose > ULN then use > 2 × pre-dose	> 1.5 × ULN, or if pre-dose > ULN then use > 2 × pre-dose
Albumin		Low only	≤ 2 g/dL	≤ 20 g/L
URINALYSIS				
Protein, Urine	UPRO	High only	If missing pre-dose then use ≥ 2, or if value ≥ 4, or if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4	If missing pre-dose then use ≥ 2, or if value ≥ 4, or if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4
Blood, Urine	UBLD	High only	If missing pre-dose then use ≥ 2, or if value ≥ 4, or if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4	If missing pre-dose then use ≥ 2, or if value ≥ 4, or if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4
Leukocyte Esterase, Urine	ULEUK	High only	If missing pre-dose then use ≥ 2, or if value ≥ 4, or if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4	If missing pre-dose then use ≥ 2, or if value ≥ 4, or if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4
RBC, Urine	URBC	High only	If missing pre-dose then use ≥ 2, or if value ≥ 4, or if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4	If missing pre-dose then use ≥ 2, or if value ≥ 4, or if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4
WBC, Urine	UWBC	High only	If missing pre-dose then use ≥ 2, or if value ≥ 4, or	If missing pre-dose then use ≥ 2, or if value ≥ 4, or

Table 7.6.2.4-1: Laboratory MA Criteria

Parameter	Test Code	Direction of Change	MA Criteria in US Standard Units (apply to labs collected after baseline only)	MA Criteria in SI Units (apply to labs collected after baseline only)
			if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4	if pre-dose = 0 or 0.5 then use ≥ 2, or if pre-dose = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4

7.6.2.5 ECG

All recorded ECGs (heart rate (HR), QT (QT, Bazett's corrected QT [QTcB], Fridericia's corrected QT [QTcF]), PR and QRS intervals) will be listed.

Summaries of ECG parameters (heart rate (HR), QT (QT, QTcF), PR and QRS intervals) will be tabulated by time point and treatment. Summaries of ECG parameters will include change from baseline at list of time points.

If QTcF is not available in the database, QTcF will be calculated using the reported uncorrected QT Interval and Heart Rate, and the following formula:

$$QTcF = \frac{QT}{(60/HEART\ RATE)^{1/3}}$$

Subjects with ECG intervals outside of a pre-specified range will also be listed.

The following criteria will be used to determine ECG results that are outside of a pre-specified range:

PR (msec):	Value > 200
QRS (msec):	Value > 120
QT (msec):	Value > 500 or change from baseline > 30
QTcF (msec):	Value > 450 or change from baseline > 30

7.6.2.6 Vital Signs

Values and changes from baseline for vital sign measurements will be summarized by treatment group at each scheduled time point using descriptive statistics.

7.6.2.7 Physical Examination Findings

All physical examination abnormal findings will be listed per subject.

7.6.2.8 Daily Urinary Output

Cumulative urinary output is collected daily at Hour 24, 48, 72, 96 and 120. Daily urinary output will be summarized descriptively for all treated subjects by treatment for each time point.

7.6.2.9 Oxygen Saturation

Oxygen Saturation will be summarized descriptively for all treated subjects by treatment for each time point as well as change from baseline.

[redacted]

7.7.1 7-Point Likert Scale

Both the percentage of subjects reporting moderate or markedly improved resting dyspnea and percentage of subjects reporting moderate or marked improvement using the patient global assessment on a 7-point Likert scale will be analyzed and presented in the same manner as the primary endpoint at Hours 6, 12, and 24. Missing values for the Likert scale at Hours 6, 12, and 24 will only be imputed, if a score cannot be obtained because the subject has died or is physically unable to complete the form. In these cases, a worst score imputation (i.e. -3) will be used for that time point.

7.7.2 Worsening Heart Failure and Worsening Renal Function

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. 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

Supportive evidences (new or worsening signs or symptoms, intensification of IV heart failure medications, and/or addition of mechanical support) for worsening heart failure collected in CRF page will be tabulated. Signs and symptoms of worsening heart failure and IV heart failure medications for subjects experiencing worsening heart failure will be listed.

The percentage of subjects reporting with an episode of worsening heart failure and percentage of subjects reporting worsening renal function will be analyzed and presented in the same manner as the primary endpoint.

7.7.3 Congestive Heart Failure

Shift analysis will be performed for changes in physical signs of congestive heart failure through Hour 120 to evaluate qualitative changes that occurred through Hour 120. A shift table will be generated for each physical sign to tabulate per-subject changes between the categories at baseline and at each study time point.

7.7.4 Sensory and Motor Function

Shift analysis will be performed for changes from baseline in items related to patient assessed peripheral sensory and motor function. A shift table will be generated for each item to tabulate per-subject changes between the scores at baseline and at each study time point.

7.8 Pharmacokinetics

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. In addition, a PK sample will be collected from the subject when the dose is lowered due to a safety event and also at time of early discontinuation of study drug. Pharmacokinetic parameters for BMS-986231 and BMT-284730 and other metabolites (e.g., BMT-279554 and CAR-000463) will be estimated as appropriate. The plasma concentration data will 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.

The PK population will be used for all listings. Evaluable PK population will be used for summaries and statistical analyses. Geometric mean and coefficient of variation (%CV) will also be presented for sample plasma concentration-time data. Analysis will include all analyte data in the PK dataset for BMS-986231 and metabolites of BMS-986231.

Subject plasma concentration-time profiles will be listed and summarized by treatment and nominal collection time for each analyte. Plots of mean (+SD) plasma concentration profiles versus time will be presented for each analyte, and all treatments will be superimposed on the same plot. Concentration at the end of infusion will also be summarized by treatment, which is the concentration at hour 48 for subjects completing 48 hours infusion and the concentration collected at early discontinuation for subjects not completing 48 hours infusion. The PK samples collected when the dose is lowered due to a safety event will be listed.

[redacted]

[redacted]

7.10 Outcomes Research

For the index hospitalization, length of stay from start of infusion to discharge and length of stay in the ICU/CCU will be summarized descriptively (see section 7.1, including the first and third quartiles) for all treated subjects by treatment.

Following discharge from the index hospitalization, the percentage of subjects with rehospitalizations and emergency department visits will be summarized descriptively by treatment group for heart failure or other cardiovascular disease separately through Day 32 and will be analyzed and presented in the same manner as the primary endpoint.

Rehospitalizations 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. Number of days alive and out of the hospital will also be summarized for all treated subjects by treatment.

7.11 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 (e.g. 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. In addition to the two interim analyses, safety reviews after 20 patients in Part I (Cohort 1) and after 50 patients in each part will be performed.

No adjustments to confidence limits will be made as a result of interim analyses.

8 CONVENTIONS

8.1 Safety Data Conventions

Except as noted in Section 7.6, safety data will be handled according to the BMS safety data conventions. This document includes descriptions on how to analyze AE data as well as how to handle partial dates, missing dates, and unknown end dates when analyzing safety data. If onset time of AEs is missing or incomplete, the onset date of AEs will be used to determine if the AEs will be included in the AE summary tables as follows.

- Non-serious AEs will be included in summary tables if the onset date is on or after the start date of study treatment and not later than the date of Hour 120.
- Serious AEs will be included in summary tables if the onset date is on or after the start date of study treatment and not later than the date of Day 32.

Clinically relevant hypotension defined in the primary endpoint consists of two components which are further clarified as follow:

- The component of "SBP < 90 mm Hg (confirmed by a repeated value < 90 mm Hg)" will be identified by a SBP measurement < 90 mm Hg with confirmatory SBP measurement < 90 mm Hg within 30 minutes after the initial qualifying value. If a confirmatory SBP is missing, the initial SBP will be treated as confirmed if no SBP measurement ≥ 90 mm Hg within 30 minutes exists. The assessment time of the initial SBP < 90 mm Hg will include time from start of infusion, up to and including 6 hours after end of infusion.

The confirmatory measurement should be within 15 minutes; however, a window of up to 30 minutes will be applied, to determine if a qualifying confirmatory value is obtained.

- The component of "symptoms of hypotension" will be identified by at least one symptom (other than "low blood pressure") from the CRF page collecting signs and symptoms of low blood pressure with onset time from start of infusion, up to and including 6 hours after end of infusion

This clarification is also applied to the safety endpoints "The incidence of symptomatic hypotension up to 6 hours after the end of study drug infusion, as well as the incidence of SBP < 90 mm Hg (confirmed by a repeated value)".

Subjects counted in the endpoint "Percentage of subjects with discontinuation due to symptomatic hypotension" are those who have "Hypotension" as the reason for discontinuation and have a symptom (other than "low blood pressure") from the CRF page collecting signs and symptoms of low blood pressure with onset time on or before the time of dose discontinuation.

Subjects counted in the endpoint "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" are those who have 'Hypotension' as the reason for rate reduction, infusion interruption or discontinuation.

8.2 Baseline Measurements

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

When there is a missing baseline assessment it will not be imputed, thus, subjects are excluded from any changes from baseline analysis for which they have a missing baseline value.

8.3 Hour Ranges for Analysis of Time Points

Subjects do not always adhere strictly to the visit schedule timing in the protocol. The hour ranges for the analyses of dyspnea measured by 11-point NRS and 7-point Likert scale and patient global assessment (PGA) measured by 7-point Likert scale are defined in Table 8.3-1. The hour ranges for the analyses of laboratory ECG are defined in Table 8.3-2 and 8.3-3, respectively. The hour ranges for the analyses of assessments measured at Hour 24, 48, 72, 96, and 120 (including respiratory rate and temperature) are defined in Table 8.3.4.

Table 8.3-1: Hour Ranges for Analyses of Dyspnea Measured by 11-point NRS and 7-point Likert Scale and PGA Measured by 7-point Likert Scale

Nominal Visit	Target Hour	Hour Ranges
Baseline	Pre-dose	Randomization to ≤ Hour 0
Hour 6	Start of infusion + 6	≥ Hour 3 to < Hour 9
Hour 12	Start of infusion + 12	≥ Hour 9 to < Hour 18
Hour 24	Start of infusion + 24	≥ Hour 18 to < Hour 36
Hour 48	Start of infusion + 48	≥ Hour 36 to < Hour 60
Hour 72	Start of infusion + 72	≥ Hour 60 to < Hour 96
Hour 120	Start of infusion + 120	≥ Hour 96 to ≤ Hour 132

Table 8.3-2: Hour Ranges for Analyses of Laboratory Measurements

Nominal Visit	Target Hour	Hour Ranges
Baseline	Pre-dose	Randomization to ≤ Hour 0
Hour 24	Start of infusion + 24	≥ Hour 12 to < Hour 36
Hour 48	Start of infusion + 48	≥ Hour 36 to < Hour 60
Hour 72	Start of infusion + 72	≥ Hour 60 to < Hour 96
Hour 120	Start of infusion + 120	≥ Hour 96 to ≤ Hour 132

Table 8.3-3: Hour Ranges for Analyses of ECG

Nominal Visit	Target Hour	Hour Ranges
Baseline	Pre-dose	Randomization to ≤ Hour 0
Hour 48	Start of infusion + 48	≥Hour 24 to < Hour 60
Hour 72	Start of infusion + 72	≥ Hour 60 to < Hour 96
Hour 120	Start of infusion + 120	≥ Hour 96 to ≤ Hour 132

Table 8.3-4: Hour Ranges for Analyses of Respiratory Rate and Temperature

Nominal Visit	Target Hour	Hour Ranges
Baseline	Pre-dose	Randomization to ≤ Hour 0
Hour 24	Start of infusion + 24	≥Hour 12 to < Hour 36
Hour 48	Start of infusion + 48	≥ Hour 36 to < Hour 60
Hour 72	Start of infusion + 72	≥ Hour 60 to < Hour 84
Hour 96	Start of infusion + 96	≥ Hour 84 to < Hour 108
Hour 120	Start of infusion + 120	≥ Hour 108 to ≤ Hour 132

Vital signs (blood pressure and heart rate) are assessed at Hours 0, 0.5, 1, 2, 4, 5 (for Part I only), 6, 8, 9 (for Part I only), 10, 12, 14, 16, 18, 20, 22, 24, 28, 32, 36, 40, 44, 48, 54, 60, 66, 72, 96, 120, and Day 32. The hour ranges for the analyses of vital signs are defined in the same manner as in Table 8.3-1 to Table 8.3-4. The hour ranges around planned measurement times are based on the midpoint between planned measurement times, for example, Hour Ranges for Hour 24 is ≥ Hour 23 to < Hour 26. Hour Ranges for Hour 120 are ≥ Hour 108 to ≤ Hour 132. The value collected at the Day 32 visit will be used for the Day 32 time regardless of time ranges.

The hour ranges for the analyses of oxygen saturation are defined in the same manner as in Table 8.3-1 for Baseline, Hours 6, 12, 24, 48, and Table 8.3-4 for Hours 72, 96, and 120.

8.4 Multiple Measurements

For longitudinal summaries of data, if there are multiple records within the same Hour ranges, then the value closest to the time of the planned time points is selected unless specified otherwise.

Laboratory Measurements

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

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

Vital Signs and ECGs

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

8.5 Pharmacokinetic Summaries

In-text Tables

For in-text pharmacokinetic tables, coefficient of variation (%CV) will be reported as integers. For other statistics except for standard deviations, values of 100 or higher will be presented as integers, values of 10 - <100 will be displayed to one decimal place, and values of 1 - < 10 will be displayed to two decimal places. Values less than 1 will be displayed to three decimal places. Ratios will also be displayed to three decimal places. Standard deviations will be reported to a precision of 1 decimal place more than the mean.

Handling of Non-Quantifiable Concentrations

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

All available plasma concentration-time data will be included in the PK data set and listed accordingly.

Treatment of Outliers

Individual plasma concentrations, if deemed to be anomalous, may be excluded from the analysis following a review of available documentation (e.g., bioanalytical report, clinical data). Any such exclusion will be clearly listed in the study report along with justification for exclusion.

Entire plasma concentration-time profiles for a subject may be excluded following review of available documentation (e.g., bioanalytical report, clinical data). However, results of analysis with and without the excluded profiles may be presented in the study report. Any such exclusion will be clearly listed in the study report along with justification for exclusion.

PK Exclusions[2]

PK Analysis, Reporting, and Exclusion criteria should follow the BMS PK Harmonization document Version 3.0.

9 CONTENT OF REPORTS

Statistical components for the clinical study report will be based on the content of this statistical analysis plan (SAP). Details of the tables, listings, and figures to be prepared for interim analyses and the final CSR will be included in a study-specific Data Presentation Plan (DPP).

[redacted]