Official Title of Study:

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

NCT Number: NCT03357731

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STATISTICAL ANALYSIS PLAN

Study-Specific SAP for CV013020

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO- AND ACTIVE CONTROLLED, CROSS-OVER PHASE 2 STUDY OF CONTINUOUS 5-HOUR INTRAVENOUS INFUSIONS OF BMS-986231 IN PATIENTS WITH HEART FAILURE AND IMPAIRED SYSTOLIC FUNCTION

Version 1.0

STATISTICAL ANALYSIS PLAN

Pre [redacted]

Study Director	Signature	Date

Approved by:

☐ Study-Sp[redacted] SAP	June Ye	[redacted]	12/6/2017
	CRS Lead	Signature	Date

[redacted]

STATISTICAL ANALYSIS PLAN

Additional signature required when changes made after the first database lock may impact the pre-specified primary and critical secondary analyses:

Approved [redacted]

(For Early Phase Standard studies, signature required only for those in which the primary endpoint does not involve formal inference; e.g., ascending dose studies)

STATISTICAL ANALYSIS PLAN
FOR

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO- AND ACTIVE-CONTROLLED, CROSS-OVER PHASE 2 STUDY OF CONTINUOUS 5-HOUR INTRAVENOUS INFUSIONS OF BMS-986231 IN PATIENTS WITH HEART FAILURE AND IMPAIRED SYSTOLIC FUNCTION

PROTOCOL(S) CV013020

VERSION # 1.0

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[redacted]

Schedule of Analyses:

There is no Data Monitoring Committee (DMC) planned for this study. Occurrence of significant safety events will be submitted for review to the independent DMC that monitors the ongoing phase 2b study, evaluating the safety, tolerability and effectiveness of BMS-986231 in a population of acute decompensated heart failure patients (NCT03016325)[1].

The final analysis will be performed following the database lock after all subjects have completed the study. No interim analyses will be performed

2 STUDY DESCRIPTION

2.1 Study Design

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

A cross-over design will be implemented in this trial; every subject will be exposed to each of the 3 interventions (BMS-986231, Nitroglycerin (NTG) and placebo) in 3 treatment periods. Each treatment period will include one intervention occurring via 5-hour infusion, followed by a washout period of at least 7 days, but no more than 4 weeks.

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

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

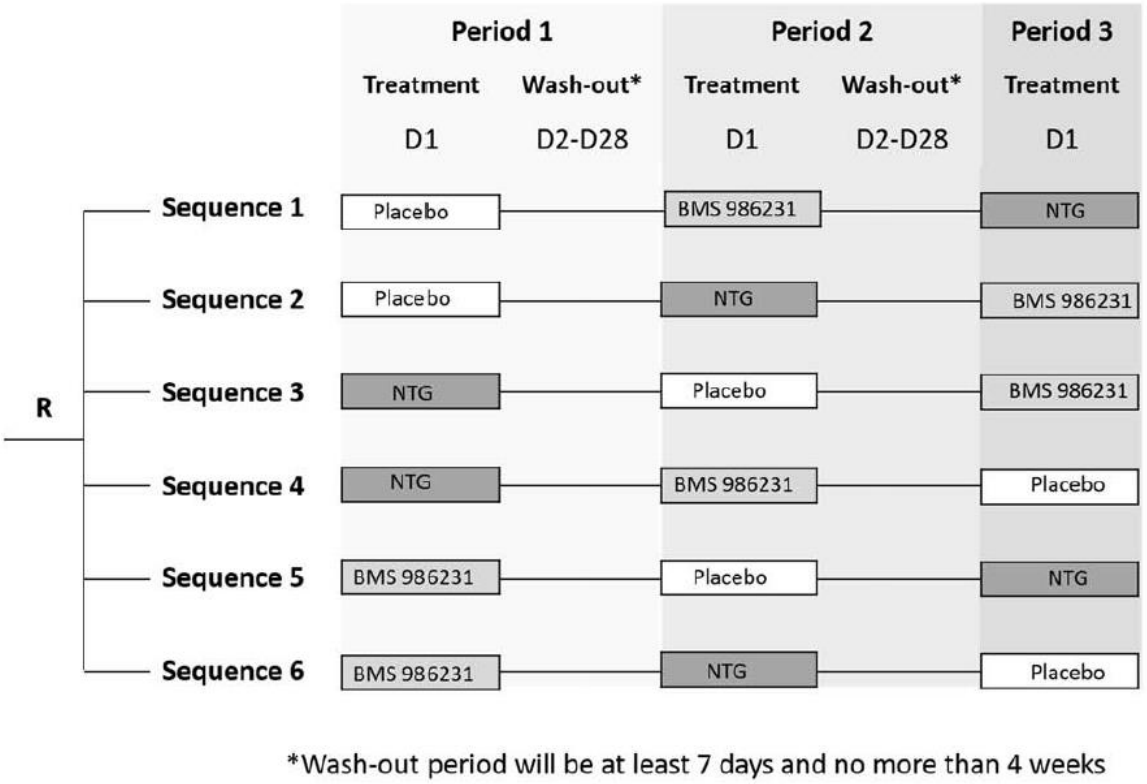
The corresponding doses of the active study medications will be:

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

In case of a decrease in systolic blood pressure, an algorithm will be used to down-titrate /interrupt or discontinue the study drug infusion (see protocol Section 7.4).

The study design schematic is presented in Figure 2.1-1.

Figure 2.1-1: Study Design



*Wash-out period will be at least 7 days and no more than 4 weeks

Screening

Screening for inclusion in the study will be performed up to 4 weeks before the first treatment day. Screening will assess the eligibility criteria including assessment of ejection fraction, suitability of echocardiography windows and image quality. After screening, study participants will be enrolled in the study according to their eligibility as per the inclusion and exclusion criteria, and will be randomized to 1 of the 6 sequences that will be conducted in parallel.

Treatment day (Day 1 of each period)

Study participants will be admitted to the study facility on the treatment day, which will be Day 1 of each of the three periods. Assessment of vital signs and laboratory tests will be performed pre-dose. In each treatment day, blood pressure and heart rate should be within the inclusion / exclusion criteria limits, and no atrial fibrillation or atrial flutter should be present in order to start the study treatment. The study drug infusion could start without waiting for the results of the laboratory assessments done in the morning of the treatment day at the study facility if the following criteria are met:

- The results of the laboratory assessment at screening / previous period are within ranges compatible with inclusion/exclusion criteria,
- The study participant was medically stable without change in medication since the screening visit / previous period.

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

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

Discharge

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

- in the opinion of the investigator an overnight stay is not warranted,
- there is no hypotension after mobilization and
- none of the following events occurred during the study drug infusion: prolonged hypotension, symptoms of hypotension, new onset of sustained arrhythmia requiring pharmacologic or other interventions, any other events of concern e.g. chest pain suggestive of ischemia.

2.2 Treatment Assignment

This study will use Interactive Response Technology (IRT): All participants will be centrally randomized using an Interactive Response Technology (IRT). Subjects will be randomized using IRT in a 1:1:1:1:1:1 ratio to one of six sequences, as shown in Figure 2.1-1, with block size of six, to ensure the number of subjects randomized to each sequence remains balanced.

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

Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with 00001, (e.g., 00001, 00002, 00003.... 00010). Those enrolled participants meeting inclusion and exclusion criteria will be eligible to be randomized. Randomization ID numbers will be assigned prior to dosing. Subjects who are re-enrolled (Protocol Section 6.4) will be assigned a new participant number. An estimated 52 subjects will be screened in order to randomize 42 subjects. Further details are provided in Section 5.

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

2.3 Blinding and Unblinding

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

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

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

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

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

The Bioanalytical Sciences section or its designate may be unblinded to the randomized treatment assignments, in order to minimize unnecessary assays of samples from subject during

the placebo treatment period. Likewise, the Biotransformation section or its designate may be unblinded, if metabolite profiling work is conducted.

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

2.4 Protocol Amendments

This statistical analysis plan (SAP) is based on the revised protocol version 02, which incorporates Amendment 02, dated 01-Sep-2017.

2.5 Data Monitoring Committee and Other External Committees

There is no Data Monitoring Committee (DMC) planned for this study. The occurrence of significant safety events will be submitted for review to the independent DMC that monitors the ongoing phase 2b study CV013011, evaluating the safety, tolerability and effectiveness of BMS-986231 in a population of acute decompensated heart failure patients (NCT03016325).

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

3 OBJECTIVES

3.1 Primary

The primary objective is to evaluate the effects of BMS-986231 on the left ventricular (LV) systolic function by SVI assessed by echocardiography compared to placebo.

3.2 Secondary

Secondary objectives include the following:

- Evaluate the effects of BMS-986231 on the left ventricular (LV) systolic function by SVI assessed by echocardiography compared to nitroglycerin (NTG).
- Evaluate the effects of BMS-986231 on selected other left ventricular systolic and diastolic indices compared to placebo and NTG:
  - LV ejection fraction
  - Mean LV power index
  - Diastolic function
  - LV global longitudinal strain

[redacted]

[redacted]

4 ENDPOINTS

4.1 Primary Endpoints

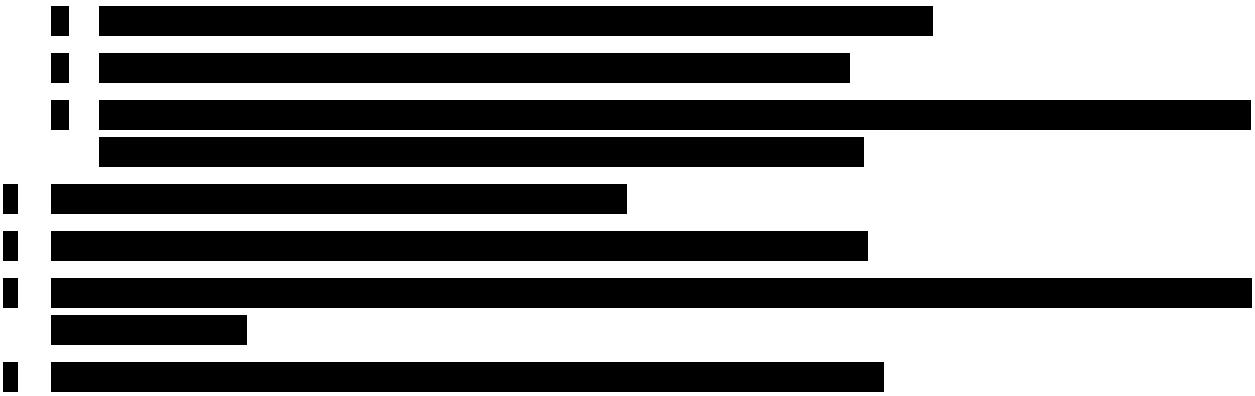
The primary endpoint is the Mean SVI derived from the velocity time integral at the left ventricular outflow tract (LVOT VTI) at the end of the 5-hours infusion of BMS-986231, versus placebo.

4.2 Secondary Endpoints

Secondary endpoints include the following:

- Mean SVI derived from LVOT VTI at the end of the 5-hours infusion of BMS-986231, versus NTG.
- Mean LVEF, computed by Simpson's method at the end of the 5-hours infusion of BMS-986231, versus placebo and NTG.
- Mean cardiac power index at the end of the 5-hours infusion of BMS-986231, versus placebo and NTG.
- Mean Diastolic indices: E/A, annular e' velocity, and E/e' ratio at the end of the 5-hours infusion of BMS-986231, versus placebo and NTG.
- Mean LV global longitudinal strain, computed using STE at the end of the 5-hours infusion of BMS-986231, versus placebo and NTG.

[redacted]



4.4 Pharmacokinetic Endpoints

- Pharmacokinetic endpoints include the Plasma concentrations of BMS-986231 and its metabolites

5 SAMPLE SIZE AND POWER

In a review of stroke volumes and SVIs from the literature, baseline SVI generally ranged from 30-40 mL/m^2, with inter-individual standard deviation (SD) of approximately 25 − 35% of the mean. Likewise, SV values generally ranged from 50-70 mL, with inter-individual SD of approximately 25 − 35% of the mean. Results from these studies also suggest intra-individual correlations in the range of 0.6 – 0.8.

Sample size calculations assume baseline SVI of approximately 30 mL/m^2, with placebo values consistent with baseline, an increase of 15% from baseline, relative to placebo, as meaningful (e.g. 4.5 mL/m^2), an inter-individual SD of 10 mL/m^2, and intra-individual correlations for the difference between placebo and HNO of 0.7. Using these assumptions, approximately 36 subjects with data from treatment periods being compared will be required to achieve a power of 90%, with a type I error probability of 0.05 (2-sided). In order to address the potential for missing data arising from dropout, an allowance of 15% subjects will be included, with a resulting target sample size of 42 subjects to be randomized. An estimated 52 subjects will be screened, in order to randomize 42 subjects. Sample sizes are calculated based on method IV from Mehrotra[2], which compares post baseline values, adjusting for the differences in the baseline value. The blinded SVI data will be reviewed after 50% of the planned treated subjects have completed treatment. BMS will consider re-estimating the sample size based on the observed SD. The review of SVI data will be repeated if necessary.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

Screening for inclusion in the study will be performed up to 4 weeks before the first treatment day. After screening, study participants will be enrolled in the study according to their eligibility as per the inclusion and exclusion criteria, and will be randomized to 1 of the 6 sequences that will be conducted in parallel.

Each sequence has 3 periods. Study participants will be admitted to the study facility on the treatment day, which will be the Day 1 of each of the three periods. Study participants will remain in the study facility for approximately 3.5 hours post-dose and discharged on the same day, unless the investigator and the study team consider that an overnight stay is warranted. The treatment day of period 1 and period 2 are followed by a washout period of at least 7 days but no more than 4 weeks.

6.2 Treatment Regimens

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

Table 5.2-1: Selection and Timing of Dose

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

Table 5.2-1: Selection and Timing of Dose

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
	20 mL/H for the rest of the 5-hour infusion		

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

6.3 Populations for Analyses

The following populations will be used for the analyses:

- **The Enrolled Population** will consist of all subjects who sign informed consent
- **The Randomized Population** will consist of all randomized subjects who have started study drug infusion in at least one treatment period. This is also known as the Intent to Treat (ITT) population. Data in this data set will be analyzed based on randomized treatments in each period.
- **The Safety Population** will consist of all subjects who take at least 1 dose of double-blind study treatment. Participants will be included in the treatment group they received in each period.
- **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

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.

In general, continuous variables will be analyzed using a mixed-effect model with sequence, treatment period, and treatment, and the difference in the treatment period baselines as a covariate. From the statistical modeling, the means, standard errors, and 2-sided 95% confidence intervals for the difference between BMS-986231 and the other treatment group will be presented. The analyses for efficacy and exploratory endpoints will use a nominal level of

α=0.05 for inference with no multiplicity adjustment. The nominal p-value for comparing two treatments will be provided as well.

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.

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

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
- Systolic blood pressure (SBP) < 115 mm Hg at screening or pre-randomization
- Violation of inclusion criterion 2 (b): Subjects do not have heart failure with reduced ejection fraction or have no LVEF on echocardiogram of 40% or less.
- Violation of exclusion criterion 1 (a): Subjects have Systolic blood pressure (SBP) < 115 mm Hg at screening or pre-randomization.
- Violation of exclusion criterion 1 (b): Subjects have heart rate < 50 beats per minute (bpm) or > 90 bpm at screening or pre-randomization.
- Violation of exclusion criterion 3 (a): Subjects have treatment with oral phosphodiesterase type 5 (PDE5) inhibitor sildenafil, vardenafil or avanafil within 24 hours of study drug infusion or treated with tadalafil within 4 days of study drug infusion.
- Violation of exclusion criterion 4 (a): Subjects have estimated glomerular filtration rate (eGFR) < 15 ml/min/1.73 m^2.

7.3 Study Population

1.1.1 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 each treatment of 5 hours infusion, both overall and according to reasons for discontinuation from the treatment, will be summarized for safety population. Subjects who have temporary interruption or down-titration of study drug but do not discontinue permanently will be analyzed 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 safety population, as overall and by treatment group.

1.1.2 Demographics and Baseline Characteristics

Frequency distributions and summary statistics for demographic and baseline variables will be presented for all enrolled subjects. Demographic variables to be summarized include: age, gender, race, ethnicity, and region.

Baseline variables to be summarized include the following:

- Physical measurements (height, body weight, body mass index)
- Vital signs (body temperature, respiratory rate, systolic and diastolic blood pressure and heart rate)

1.1.3 Physical Measurements

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

1.1.4 Medical History and Previous Medications

Medical history and previous medications taken prior to dosing will be listed for the safety population.

7.4 Extent of Exposure

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

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

- Study drug reduction: Study drug is decreased by 50% if SBP decreases to levels <90 mmHg but ≥80 mmHg. The dose cannot be subsequently increased.
- Study drug interruption: Study drug is interrupted for 1 hour if SBP decreases to <80 mmHg or symptoms of low blood pressure occur within the first 4 hours of infusion. If the SBP is ≥ 105 mmHg after one hour interruption, the study drug could be resumed at 50 % of the dose to complete 5-hours of effective study drug infusion.
- Study drug discontinuation: Study drug will be permanently discontinued if SBP remains < 105 mmHg after 1 hour interruption or if SBP decreases to levels <80 mmHg or symptoms of low blood pressure occur after 4 hours of infusion.

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

Study drug administration and randomization schedule will be documented as per subject listings. The number and percentage of subjects with dose interruptions, dose reductions, and

dosing discontinuations will also be summarized and listed by treatment group for the safety population.

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.

7.5 Efficacy

7.5.1 Primary Efficacy Analysis

SVI derived from the velocity time integral at the left ventricular outflow tract (LVOT VTI) at the end of the 5-hours infusion of treatment will be summarized descriptively for all randomized subjects by treatment group.

SVI will be assessed using a contrast comparing placebo and BMS-986231. We follow the linear model proposed by Jemielita et al[3], which includes sequence and treatment and the difference in the treatment period baselines as a covariate. Jemielita et al demonstrated that modelling certain linear combinations of baseline values as covariates increases the power of the test for a difference in outcomes by treatment. In this study, the difference in baseline values among the treatments being compared will be considered according to this strategy. They further demonstrated that the model will give equivalent inference as in an ordinary least squares (OLS) model for difference of treatment effects, under the assumption of unstructured covariance structure. The Kenward-Roger approximation for the degrees of freedom will be specified for the model.

Estimation of the variance covariance will be based on unstructured (UN) R matrix assuming no common variances or covariances.

Let

$$X_{ik}=(X_{iPk},\ X_{iNk},\ X_{iTk})^T$$

$$Y_{ik}=(Y_{iPk},\ Y_{iNk},\ Y_{iTk})^T$$

be distinct 3-length vectors of baseline SVI and end of infusion SVI, respectively. The subscript $i=1,...6$ indexes the sequences, and $P,\ N,\ T$ represent Placebo, NTG and BMS 986231. Moreover, $k=1,...7$ indexes subject k in sequence i.

We fit the following linear mixed model:

$$(Y_{iTk}-Y_{iPk})|(X_{iTk}-X_{iPk})=(\tau_T-\tau_P)+(\Upsilon_{iT}-\Upsilon_{iP})+(\beta_T-\beta_P)(X_{iTk}-X_{iPk})+(\varepsilon_{iTk}-\varepsilon_{iPk}),$$

where $\tau_T-\tau_P$ is the difference of treatment effects of BMS-986231 and Placebo, $\Upsilon_{iT}-\Upsilon_{iP}$ is the difference of treatment effect of BMS-986231 and Placebo within sequence i, $\beta_T-\beta_P$ is the regression coefficient, and $\varepsilon_{iTk}-\varepsilon_{iPk}$ is the variance term.

The hypotheses of interest are:

$$H_0: \tau_T - \tau_P = 0$$

$$H_A: \tau_T - \tau_P \neq 0.$$

The mean SVI at the end of 5-hour infusion of BMS-986231 versus Placebo, corresponding standard error, p value, and 95% confidence interval will be calculated by the below SAS code and presented. Considering the sample size is small, the Kenward-Roger degree of freedom is used to adjust the standard error of treatment effect.

```
PROC MIXED DATA=EXAMPLE_DATA;
CLASS sequence;
MODEL ydiff TP = sequence xdiff TP / DDFM=KENWARDROGER;
ESTIMATE 'tau_T - tau_P' intercept 1 xdiff_TP / CL;
run;
```

SVI will be summarized and listed for all randomized subjects as overall and by treatment.

7.5.2 Secondary Efficacy Analysis

Using the same model as in the primary analysis, this analysis will be repeated for the secondary endpoints listed below and will also examine the comparison of BMS-986231 vs NTG in addition to BMS-986231 vs Placebo.

- Mean SVI derived from LVOT VTI at the end of the 5-hours infusion of BMS-986231, versus NTG.
- Mean LVEF, computed by Simpson's method at the end of the 5-hours infusion of BMS-986231, versus placebo and NTG.
- Mean cardiac power index (CPI) at the end of the 5-hours infusion of BMS-986231, versus placebo and NTG. Cardiac power index is calculated by the following equation: CPI [W/m^2] = mean aortic pressure [mmHg] × cardiac output [L/min] / body surface area [m^2] × 0.0022.
- Mean Diastolic indices: E/A, annular e' velocity, and E/e' ratio at the end of the 5-hours infusion of BMS-986231, versus placebo and NTG.
- Mean LV global longitudinal strain, computed using STE at the end of the 5-hours infusion of BMS-986231, versus placebo and NTG.

The secondary endpoints will be summarized and listed for all randomized subjects as overall and by treatment.

7.6 Safety

All safety presentations will be based on the Safety Population.

7.6.1 Deaths

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

7.6.2 Serious Adverse Events

All reported serious adverse events (SAEs) will be listed by System Organ Class (SOCs) and Preferred Terms (PTs) for all safety population subjects. SAEs must be collected from the date of informed consent and will be assessed up to 30 days after the end of infusion of the last period.

7.6.3 Adverse Events

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

Non-serious AEs with onset time from the start of study drug infusion, until 24 hours after end of infusion in each treatment period of dosing in each period 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.

7.6.4 Clinical Laboratory Evaluations

The results of all protocol-specified clinical laboratory tests will be listed. Scheduled laboratory measurements 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 6.6.2.4-1), 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 6.6.2.4-1: 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	AST	High only	> 3 × ULN, > 5 × ULN, > 10 × ULN	> 3 × ULN, > 5 × ULN, > 10 × ULN

Table 6.6.2.4-1: 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)
Aminotransferase				
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
Blood Urea Nitrogen	BUN	High only	>2 × ULN	>2 × ULN
Serum Creatinine	CREAT	High only	> 1.5 × ULN	> 1.5 × 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

Table 6.6.2.4-1: 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)
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
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 missing pre-dose then use ≥ 2, or if value ≥ 4, or if pre-dose = 0 or 0.5 then use ≥ 2, or

Table 6.6.2.4-1: 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 = 1 then use ≥ 3, or if pre-dose = 2 or 3 then use ≥ 4	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 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

7.6.5 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:

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

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

7.6.6 Vital Signs

Vital sign measurements will be summarized by treatment group at each scheduled time point using descriptive statistics.

7.6.7 Physical Examination Findings

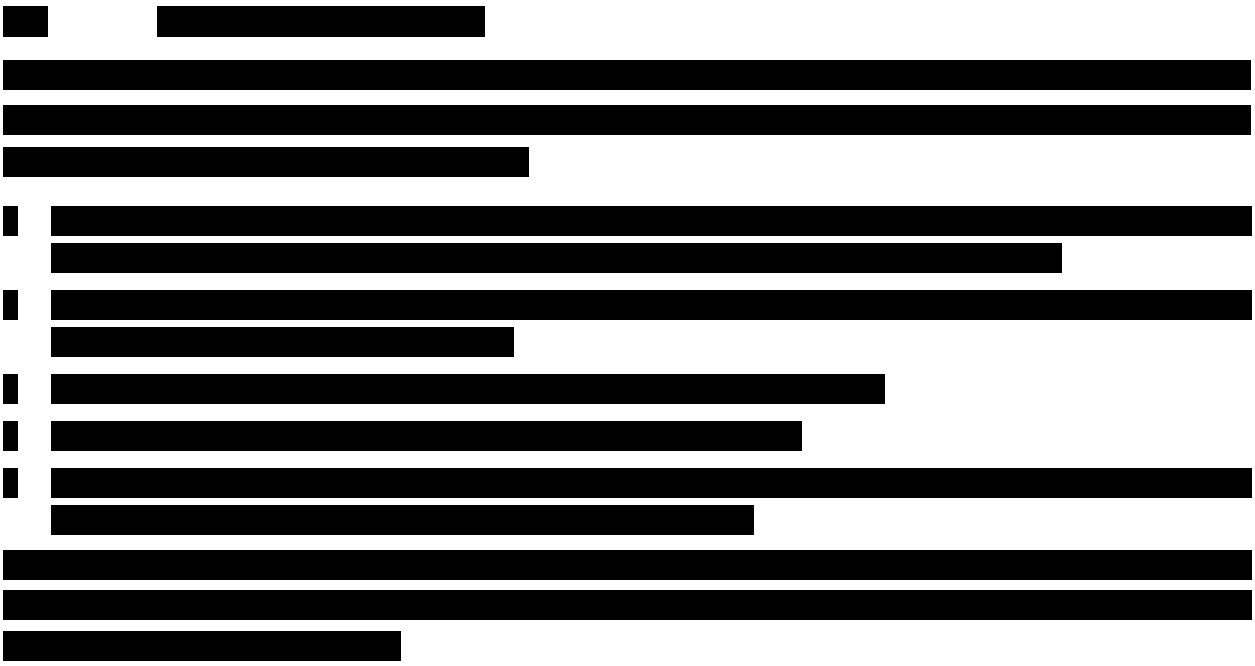
All physical examination abnormal findings will be listed per subject.

7.6.8 Daily Urinary Output

Urinary output is collected from start of infusion to 3 hours after end of infusion in each treatment period. Daily urinary output will be summarized descriptively for all safety population by treatment for each time point.

7.6.9 Oxygen Saturation

Peripheral Oxygen Saturation is collected prior to the infusion and after end of infusion in each treatment period. Oxygen Saturation will be summarized descriptively for all safety population by treatment for each time point as well as change from baseline.



7.8 Pharmacokinetics

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

The PK population will be used for all listings. The 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 5 for subjects completing 5 hours infusion and the concentration collected at early discontinuation for subjects not completing 5 hours infusion. The PK samples collected when the dose is lowered due to a safety event will be listed.

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[4]. 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/time is on or after the start of the study drug infusion until 24 hours after endo f infusion in each treatment period of dosing.
- Serious AEs will be included in summary tables if the onset date/time is on or after the start date of study drug infusion until 30 days after the end of infusion of the last period.

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.

8.3 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.

8.4 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[5]

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]