Official Title of Study:

An Investigational Study of Continuous 8-Hour Intravenous Administrations of BMS-986231 in Participants With Heart Failure and Reduced Heart Function Given a Standard Dose of Loop Diuretic

NCT Number: NCT03730961

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Statistical Analysis Plan

Sponsor:	Bristol-Myers Squibb Research and Development
Protocol No:	CV013-034
Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Cross-over Phase 2 Study of Continuous 8-Hour Intravenous Infusions of BMS-986231 in Patients with Heart Failure and Impaired Systolic Function Given a Standard Dose of Loop Diuretic
PRA Project ID:	BMS001PC-180016
Version Date:	22-Jan-2020

1.0 Approvals

The undersigned have approved this Statistical Analysis Plan for use in this study.

2.0 Table of Contents

3.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under Bristol-Myers Squibb Research and Development (BMS) Protocol CV013034.

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the plan has been developed using the protocol dated 15-Apr-2019 (including all amendments up to this date) and the final eCRF(s) dated 22-Oct-2018.

An approved and signed SAP is a requirement for database lock.

This SAP only covers the results that will be processed by the PRA Early Development Services (EDS) Biostatistics Department.

PRA EDS will perform the efficacy, pharmacokinetic (PK), pharmacodynamic (PD), biomarker and safety and tolerability evaluations.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. Any post-hoc or unplanned analyses, or significant changes from the planned analysis in this SAP performed to provide results for inclusion in the clinical study report (CSR) but not included in this SAP, will be clearly identified in the CSR. Changes to planned analyses do not require an updated SAP but should be discussed with the sponsor and included in the CSR if significant.

4.0 Changes from Previous Version of Approved SAP

This is the first version of the SAP.

5.0 Study Objectives

5.1 Primary

Evaluate the effects of HNO donor BMS-986231 on 4-hour urine output in patients with HFrEF after administration of 40 mg of IV furosemide.

5.1.1 Primary Endpoints

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

5.2 Secondary

Assess the effect of BMS-986231 on fractional excretion of Na (FeNa)

Assess the effect of BMS-986231 on fractional excretion of K (FeK)

Assess the effects of BMS-986231 on furosemide urinary and plasma concentration and the ratio urinary sodium to urinary furosemide

Assess safety of BMS-986231

5.2.1 Secondary Endpoints

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

5.2.2 Safety Endpoint

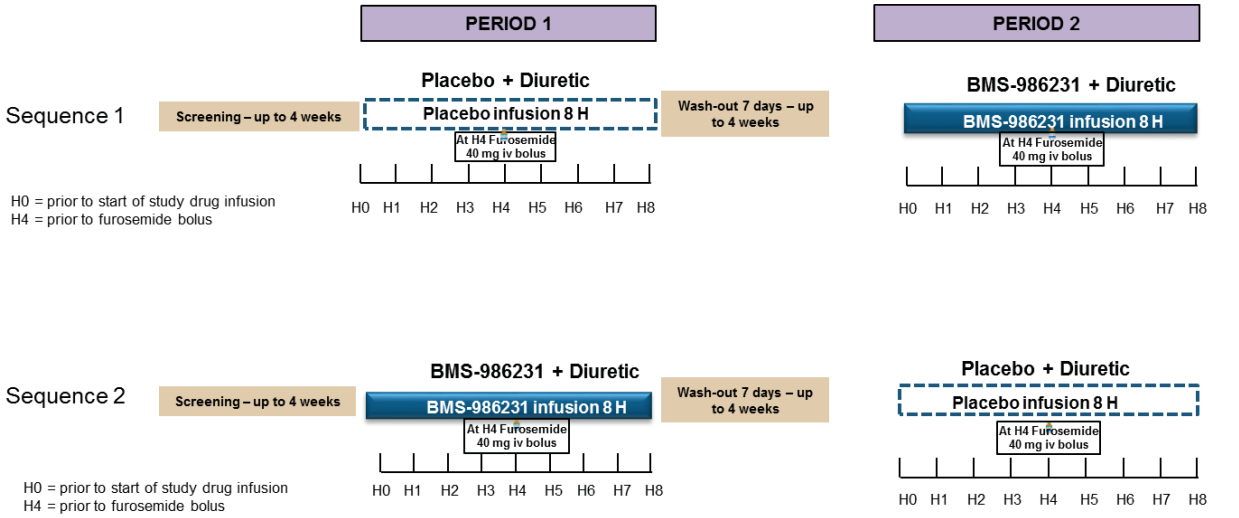
Clinically relevant hypotension (defined as SBP < 90 mmHg or symptomatic hypotension) during infusion, incidence of AEs, abnormal clinical laboratory values, vital signs, ECGs, telemetry, physical examinations.

[redacted]

6.0 Study Design

This is a double blinded, randomized, two-way cross-over, placebo-controlled study to evaluate the effects of HNO donor BMS-986231 on 4-hour urine output in HFrEF patients after administration of 40 mg of IV furosemide. The study consists of 2 one-day treatment periods (BMS-986231 or placebo) separated by a washout period of at least 7 days (Day 2 to at least Day 8), but no more than 4 weeks. Each period includes 8-hour infusion. A standard dose of 40 mg IV furosemide will be administered by IV bolus injection at the midpoint (4 hour, H4) of an 8-hour infusion. Screening for inclusion in the study will be performed up to 4 weeks before the first treatment day (Day 1 of the first period). Approximately 20 subjects will be included. The total duration of the study will be approximately 8 weeks.

Study Design Schematic from Protocol:



6.1 Sample Size Considerations

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

Normal healthy volunteers have a urinary output around 0.5-1.0 mL/kg/H (40-100 mL/H), which could be decreased in people over 65 years old or patients with HF at around 0.2-0.5 mL/kg/H (20-40 mL/H). Patients with HF given a bolus of IV loop diuretics is estimated to have their diuresis increased to 250-300 mL/H in the 4 hours following the administration. Assuming the standard deviation of urine output change is 20~35 mL/H based on the estimated range of the changes, with 20 patients, the study will be able to demonstrate a 20% increase in urinary output compared to placebo, with 90% power.

6.2 Randomization

The subjects were randomized by the Biostatistics Department of the EDS group of PRA Health Sciences using PROC PLAN in SAS. Subjects (N=20 plus 4 additional) were assigned to one of the two sequences active treatment/placebo or placebo/active treatment with a 1:1 allocation ratio. An additional randomization was run a second time for the second site (Richmond, London) which was only added to the study when it was already running at the first site (NHS, Glasgow). For details, please see Global Note to File no.2.

Subject numbers that were used are R01-R24 and S01-S24. Participants will not be replaced if they are discontinued from the study.

7.0 Overview of Planned Analysis

7.1 Changes from Protocol

There are no changes from protocol

7.2 Planned Analyses

7.2.1 Preliminary Analysis

No preliminary analysis is planned.

7.2.2 Topline Results

Topline tables, figures, and listings (TFLs) will be provided after database lock. Topline TFLs will be determined by the Biostatistics Asset Lead and Clinical Pharmacology Asset Lead prior to programming commencing and will be the minimal set of TFLs needed to analyze key endpoints.

7.2.3 Final Analysis

The full set of draft TFLs will be provided after topline TFLs. After comments have been incorporated on the draft TFLs, the TFLs will be approved by the Biostatistics Asset Lead and incorporated in the CSR.

8.0 Definitions and General Analysis Methods

8.1 Analysis Data Presentation

8.1.1 Rounding

In listings, data will be presented with the same precision as the original data. Derived data will be rounded for presentation purposes.

For all summaries (with the exception of PK), the mean will be presented to 1 decimal greater than the original data, the SD to 2 decimals greater than the original data, and the median, minimum (min) and maximum (max) values will be presented to the same number of decimal places as the original data.

For PK summaries, mean, SD, median, min, and max values ≥ 100 will be presented as integers, values < 100 but ≥ 10 will be presented with 1 decimal, values < 10 but ≥ 1 will be presented with 2 decimals, and values < 1 will be presented with 3 decimals. Ratios will be presented with 3 decimals. Coefficient of variation (%CV) will be presented with 1 decimal.

For listing presentation purposes, PK parameters will be rounded in the same manner as noted above for summaries.

P-values will be reported to 4 decimal places; p-values less than 0.0001 will be reported as p <0.0001.

8.1.2 Imputation

Unless otherwise noted, data will not be imputed.

8.1.3 Descriptive Statistics

Unless otherwise indicated in specific data type sections, continuous variables will be summarized with the following descriptive statistics: n (number of observations), (arithmetic) mean, SD, median, min, and max.

Categorical data will be summarized with frequencies and percentages. Percentages by categories will be based on the number of subjects within a treatment group. Percentages will be rounded to 1 decimal, except 100% which will be displayed without any decimal places. Percentages will not be displayed for zero counts. Categories will be presented in the tables exactly as they appear in the CRF / Database.

8.1.4 Pooling

No data will be pooled for this study.

8.1.5 Unscheduled Measurements

Unscheduled measurements will be included in the listings. With the exception of unscheduled measurements used for baseline, unscheduled measurements will be excluded from the descriptive statistics and statistical analysis.

8.2 Analysis Data Definitions

8.2.1 Baseline Definition

Unless otherwise stated, baseline for post-dose evaluations is defined as the last observation recorded before the study drug administration in a period. The last observation can be an unscheduled / repeated measurement.

8.2.2 Treatment/Subject Grouping

Label	Grouping
Study Drug	BMS-986231 or Placebo
Treatment	BMS-986231: BMS-986231 12 µg/kg/min for 8 hours (20 mL/H), single infusion IV Placebo: Placebo 20 mL/H for 8 hours, single infusion IV Furosemide: Furosemide 40 mg, single IV bolus

8.2.3 Common Variable Derivations

Variable	Dataset	Definition/Calculation
Change from Baseline	All	Post-dose Observation minus Baseline Observation
Analysis Period	All	Interval of time during which treatment is constant.
TEAE	AE	AE is a TEAE if the AE Date/Time is greater than or equal to the first Dose Date/Time

8.2.4 QC

The analysis datasets and the TFLs will be QC'd according to the PRA EDS QC plan that is developed according to the EDSREP 009 SOP.

8.2.4.1 Critical Data

The QC plan requires datasets be classified as critical or non-critical. The datasets considered critical are subject level, efficacy, and adverse events (ADSL, ADEFF, and ADAE).

8.2.5 ADaM Datasets and Metadata

The analysis datasets will be generated in accordance with Clinical Data Interchange Standard Consortium (CDISC) Analysis Data Model (ADaM) Version 2.1.

ADaM compliant datasets will be delivered to the sponsor. A define.xml file version 2 with the corresponding metadata will be included. Analysis results metadata are excluded.

8.3 Software

The statistical analysis and reporting will be done using SAS® for Windows™ Version 9.4 or higher (SAS Institute, Inc.).

PK parameter calculations will primarily be done using Phoenix® WinNonlin® Version 8.1 or higher (Certara, Inc.). Additional PK computations may be performed in SAS®.

8.4 Statistical Methods

8.4.1 Statistical Outlier Determination

No statistical outlier analysis is planned.

8.4.2 Predetermined Covariates and Prognostic Factors

There are no predetermined covariates or prognostic factors.

8.4.3 Hypothesis Testing

Unless otherwise stated, all significance testing will be 2-sided at the significance level of 0.05.

9.0 Analysis Sets

Analyses	Enrolled	Randomized	Treated per protocol	Safety
Disposition	✓			
Baseline Characteristics		✓	✓	
Safety Assessments				✓
Primary Efficacy Analysis			✓	
Other Efficacy Analysis			✓	
PK Analysis			✓	

9.1 Enrolled

All participants who sign informed consent.

9.2 Randomized

All randomized subjects who have started study drug infusion in at least one treatment period. This is also known as the Intent to Treat (ITT) population. Data in this data set will be analyzed based on randomized sequence of treatments.

9.3 Treated (per protocol)

All randomized participants who were given both study treatments and completed the study as per protocol. Participants will be included in the treatment group they received in each period.

9.4 Safety

All randomized participants who take at least 1 dose of double-blind study treatment. Participants will be included in the treatment group they received in each period.

10.0 Subject Disposition

The number of subjects in each analysis set will be presented.

The number and percentage of subjects who withdrew from the study prematurely and a breakdown of the corresponding reasons for withdrawal will be presented by analysis set. Percentages will be based on the total number of subjects in the analysis set.

11.0 Protocol Deviations

Protocol deviations will be collected and entered into the Clinical Trial Management System (CTMS) per clinical monitoring Standard Operating Procedures. From CTMS, protocol deviations will be pulled into SDTM. Important protocol deviation data will be listed by subject.

12.0 Demographic and Baseline Characteristics

12.1 Demographics

Subject demographics will be summarized descriptively for the Randomized and Per Protocol analysis sets. The summary will include the subjects' age (years), sex, race, ethnicity, weight (kg), height (cm), and BMI (kg/m^2). Any measurements will be included from assessments performed during the Screening Visit. .

All demographic data, as collected during the screening visit, will be listed by subject.

12.2 Medical History

Medical history including disease under study will be categorized by preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be listed by subject.

12.3 Other Baseline Characteristics

All screening criteria data collected on the CRF (including failed eligibility criteria) will be listed by subject.

Childbearing Potential will be listed.

[redacted]

14.0 Treatment Compliance and Exposure

The number and percentage of subjects receiving full dose of study drug will be summarized by sequence in periods 1 and 2 for the safety analysis set.

All study drug administration data will be listed by subject.

15.0 Efficacy Analyses

15.1 Effect of BMS-986231 on urine output

All primary efficacy analyses will be performed using the treated (per protocol) population.

Urinary output will be listed by timepoint.

The volumes (total within 4 h after furosemide dosing, total within 4 h before furosemide dosing, total within 8 h after start of BMS-986231/placebo dosing and difference of totals after and before furosemide dosing) after BMS-986231 and after placebo will be calculated per patient.

Descriptive statistics (n, mean, SD, %CV, median, min, and max) will be used to summarize the absolute difference between the volumes under BMS-986231 dosing and under placebo and the percent change from placebo under BMS-986231 dosing of urinary output by treatment.

Plots of the arithmetic mean urinary output + SD by scheduled sampling times will be provided by treatment. Bar plots showing the arithmetic mean urinary output and the individual urinary output by interval and treatment will be provided. These plots will show time in hours. The plots will match the summary table results. Plots will be presented to the last scheduled time point.

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

The SAS PROC TTEST code is as follows:

```
proc ttest data = volume;
   PAIRED BMS-986231*placebo;
run;
```

Paired profiles and Q-Q plot of the urinary output under BMS-986231 and placebo treatment will be provided for a visual representation of the data.

15.2 Effect of BMS-986231 on fractional excretion

Secondary efficacy analyses will be performed using the per protocol population.

The fractional excretion (total within 4 h after furosemide dosing, total within 4 h before furosemide dosing, total within 8 h after start of BMS-986231/placebo dosing and difference of totals after and before furosemide dosing) of Na (FeNa) and K (FeK) after BMS-986231 and after placebo will be calculated per patient.

Descriptive statistics (n, mean, SD, %CV, median, min, and max) will be used to summarize the absolute difference between the excretion under BMS-986231 dosing and under placebo and the percent change from placebo under BMS-986231 dosing of fractional excretion by treatment.

Bar plots showing the arithmetic mean urinary output and the individual urinary output by interval and treatment will be provided.

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

Paired profiles of fractional excretion will be provided for a visual representation of the data.

15.3 Effect of BMS-986231 on furosemide concentration

Furosemide urinary and plasma concentrations and the ratio of urinary sodium to urinary furosemide will be calculated at each time point over 4-hour urine/plasma collection after a bolus injection of 40 mg furosemide while receiving BMS-986231 or placebo

Descriptive statistics (n, mean, SD, %CV, median, min, and max) will be used to summarize the absolute difference and the percent change from placebo of furosemide urine concentration, furosemide plasma concentration and the ratio of urinary sodium to urinary furosemide at 8 h by treatment.

Paired profiles of furosemide urine concentration, furosemide plasma concentration and the ratio of urinary sodium to urinary furosemide (4 h after furosemide dosing) will be provided for a visual representation of the data.

[redacted]

[redacted]

16.0 Pharmacokinetic Analyses

The PK summaries described in this section will be created using the Randomized analysis set.

16.1.1 Plasma Concentrations

Descriptive statistics (n, mean, SD, CV%, geometric mean, median, min, and max) will be used to summarize the plasma concentrations of Furosemide, BMS-986231 (and its metabolites) at each scheduled time point (see table in Appendix 3).

Plasma concentrations below the limit of quantification (BLQ) will be set to missing in the computation of mean concentration values. No descriptive statistics will be provided if more than half of the subjects have values BLQ.

All individual subject plasma concentration data will be listed.

16.1.2 Urine Concentrations

Urine recovery of Furosemide, BMS-986231 (and its metabolites) will be calculated per interval and cumulative. Parameters will be calculated as follows for 4-10 h for furosemide and for 0-10 h for BMS-986231 and metabolites:

Parameter	Description	SAS Programming Notes
Ae(0-T)	Cumulative amount of drug excreted unchanged into urine to time t (last scheduled sample). The amounts recovered in urine over a collection interval are calculated by multiplying the urine concentrations for each analyte by the total volume/weight of the sample collected during that interval. The sum of the amount recovered for all intervals is calculated to obtain the total amount recovered in urine, obtained by adding the amounts excreted over each collection interval.	Summation i = 1 to n of (Concentration (ng/mL) t_{i-1}-t_i*volume(mL)t_{i-1}-t_i)

Parameter	Description	SAS Programming Notes
Fe	Fraction (represented in %) of the administered dose excreted unchanged into urine. The sum of the percentage of dose for each analyte for all intervals will be calculated to obtain the total percentage urinary recovery.	(Ae(0-T)/Dose)*100

All individual subject urine parameters (interval times, concentration, volume, amount excreted in interval) data will be listed.

Otherwise urine parameters will be summarized as described above.

Safety Analyses

The safety summaries described in this section will be created using the Safety set.

16.2 Safety Variables

The following safety variables will be included:

- Adverse Events
- Clinical Laboratory Evaluations
- Vital Signs
- Electrocardiograms

16.2.1 Adverse Events

An AE is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant that does not necessarily have a causal relationship with treatment. Treatment-emergent adverse events (TEAEs) are those which occur after the first dose of study drug. All TEAE summaries will be presented alphabetically by system organ class, with preferred terms sorted in decreasing order of frequency within each system organ class based on MedDRA dictionary.

For treatment period assignment, the following rules will be applied:

- TEAEs occurring following dosing in period 1 but before dosing in period 2 will be attributed to the drug administered in period 1.
- TEAEs occurring following dosing in period 2 will be attributed to the drug administered in period 2.

If the time is missing for an AE on a dosing day, then the AE will be attributed to the treatment period of the treatment given on that day.

The following missing data will be imputed (for calculations only) as defined:

- Missing AE start and / or end times for the calculation of onset and duration will be assumed to be at 00:01 for a start time and 23:59 for end times
- Missing AE severity or relationship will be left as missing
- Missing AE start times for the determination of treatment emergence will be assumed to occur after treatment unless partial date documents the AE as happening prior to treatment
- Missing AE start times for the determination of treatment assignment will be assumed to occur after treatment on the recorded date one minute after dosing
- Missing AE start date will be assumed to be after treatment for the determination of TEAE but will not be attributed to a specific treatment

A summary of the number and percentage of subjects reporting AEs, TEAEs by severity, serious AEs (SAEs), and who discontinue study drug due to an AE will be presented by treatment and overall.

A summary of the number and percentage of subjects reporting each TEAE will be presented by treatment and overall. Counting will be done by subject only, not by event; subjects will only be counted once within each body system or preferred term.

A summary of the number and percentage of subjects reporting each TEAE will be presented by relationship to BMS-986231 (as recorded on the CRF) and by treatment and overall. Subjects with multiple events will be counted under the category of their most-related event within each system organ class or preferred term.

A summary of the number and percentage of subjects reporting each TEAE will be presented by relationship to Furosemide (as recorded on the CRF) and by treatment and overall. Subjects with multiple events will be counted under the category of their most-related event within each system organ class or preferred term.

A summary of the number and percentage of subjects reporting each TEAE will be presented by severity (as recorded on CRF) and by treatment and overall. Subjects with multiple events will be counted under the category of their most severe event within each system organ class or preferred term.

All AEs (including non-treatment-emergent events) recorded on the eCRF will be listed by subject.

A separate listing of AEs leading to study drug discontinuation will be provided by subject.

16.2.2 Deaths and Serious Adverse Events

A listing of deaths and other SAEs will be provided by subject.

16.2.3 Laboratory Data

Clinical laboratory data will be presented using Système International (SI) units from the study data tabulation model (SDTM) Controlled Terminology.

A descriptive statistics summary of continuous laboratory results for chemistry and hematology and derived changes from baseline will be provided by scheduled time point.

All laboratory data will be listed by subject, including laboratory variables not listed in the protocol.

A separate listing of out-of-range values will also be provided. Normal ranges will be used directly from the clinical laboratory and will be included in the listings for reference.

Results from pregnancy tests will be listed.

16.2.4 Vital Signs

A descriptive statistics summary of vital signs and derived changes from baseline will be provided by treatment and scheduled time point.

All vital signs data will be listed by subject. A separate listing of hypotension will be provided.

16.2.5 Electrocardiograms

The observed measurements for all ECG parameters and the corresponding abnormalities will be listed for all timepoints. The means of triplicate measurements for continuous parameters and the change from baseline of the mean triplicate measurements at each scheduled timepoint will be listed by subject.

Descriptive statistics will be provided to summarize mean ECG parameters (observed and changes from baseline) by treatment and scheduled time.

16.2.6 Physical Examinations

All physical examination data will be listed by subject.

[redacted]

Appendix 1: Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
ADaM	Analysis data model
BLQ	Below the limit of quantification
BMI	Body mass index
BMS	Bristol-Myers Squibb
CDISC	Clinical Data Interchange Standard Consortium
CI	Confidence interval
CSR	Clinical study report
CTMS	Clinical Trial Management System
CV	Coefficient of variation
DDT	Data definition table
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Early Development Services
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
SAP	Statistical analysis plan
SAE	Serious adverse event
SDTM	Study data tabulation model
TEAE	Treatment-emergent adverse event
TFL(s)	Tables, figures and listings
WHO	World Health Organization

Appendix 2: Schedule of Activities from Protocol

Table 1: Screening Procedural Outline (CV013-034)

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

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

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

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

Procedure	Treatment Period			Notes
	Period 1 Day 1	Washout (7-28 days)	Period 2 Day 1	Washout between periods should be at least 7 days and no more than 4 weeks.
				For each period, subjects must remain for at least 3.5 hours after the end of infusion. Patients may stay overnight or may be discharged the same day 3.5 hours after end of infusion if certain conditions are met
Laboratory Tests				
Hematology and Serum Chemistry	X		X	Laboratory tests will be performed in the morning of each treatment day (H0 [before start of infusion], H4 [just before furosemide bolus], and H8).
Pregnancy Test (WOCBP only)	X		X	
Blood sampling for PK (furosemide and BMS-986231 [and its metabolites])	X		X	Blood sampling for PK will be done at H0 (before start of infusion), H2 and at H4 hours (just before furosemide bolus), H5, H6, H8 (or end of infusion) and H10 (2 hours after the end of the infusion) in each treatment period. In addition, PK samples should be taken when the dose is lowered or discontinued
Blood sampling for Na, K, bicarbonate, creatinine, and eGFR	X		X	Blood sampling for Na, K, bicarbonate, creatinine, and eGFR will be done at H0 (before start of infusion), H4 (just before furosemide bolus), H5, H6, H7, H8 (or end of infusion) in each treatment period.
Urine sampling for furosemide and BMS-986231 (or its metabolites)	X		X	Urine samples can be taken from the urine collection intervals done for the urinary output. An aliquot for both sets of metabolites and a back-up will be required for the analysis.
Urine sampling for Na, K, P, Cl, creatinine and bicarbonate concentrations	X		X	Urine samples can be taken from the urine collection intervals done for the urinary output.
Efficacy Assessments				
Urinary output	X		X	Prior to start of infusion, patients will be asked to void and urine collected. A bladder scan (ultrasound) could be performed to ensure adequate bladder emptying. Patients will be asked to void at least every 2 hours during the first 4 hours post-start infusion and before furosemide bolus, and at least hourly from 4 to 8 hours post-start infusion. A second bladder scan could be performed at H8 (8 hours after start of infusion and just after study drug discontinuation and after the void).

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

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

Appendix 3: Blood Sampling and Urine Collection Intervals for PK and Efficacy

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

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

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

[b] just before furosemide bolus

[c] EOI=End of Infusion, This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

Time points for urine collection intervals for Urine Output and Assessment of Furosemide, BMS-986231, K, Na, P, Bicarbonate, Creatinine, and Cl are as follows.

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

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

[b] just before furosemide bolus

[c] EOI=End of Infusion, This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

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Appendix 4: List of Tables, Figures, and Listings

List of Tables and Figures:		
Output	**Title**	**Analysis Set**
Section 14.1 – Disposition and Demographic Data		
Table 14.1.1	Summary of Analysis Sets	All Subjects
Table 14.1.2	Summary of Subject Disposition	All Subjects
Table 14.1.3.1	Summary of Demographics	Randomized
Table 14.1.3.2	Summary of Demographics	Per Protocol
Table 14.1.4	Summary of Dosing	Safety
Section 14.2 – Efficacy Data		
Table 14.2.1.1	Summary of Urinary Output	Per Protocol
Figure 14.2.1.2	Plot of Mean (+SD) Urinary Output over Time	Per Protocol
Figure 14.2.1.3.1	Barchart of Mean Urinary Output over Time	Per Protocol
Figure 14.2.1.3.2	Barchart of Individual Urinary Output over Time	Per Protocol
Table 14.2.1.4	Statistical Analysis of the Volumes of Urinary Excretion	Per Protocol
Figure 14.2.1.5	Plot of Paired Urinary Output by Treatment	Per Protocol
Figure 14.2.1.6	Q-Q-Plot of Difference BMS-986231 – Placebo	Per Protocol
Table 14.2.2.1	Summary of Fractional Excretion of FeNa and FeK	Per Protocol
Figure 14.2.2.2.1	Barchart of Mean Fractional Excretion over Time	Per Protocol
Figure 14.2.2.2.2	Barchart of Individual Fractional Excretion over Time	Per Protocol
Table 14.2.2.3	Statistical Analysis of the Fractional Excretion	Per Protocol
Figure 14.2.2.4	Plot of Paired Fractional Excretion	Per Protocol
Table 14.2.3.1	Summary of Natriuresis	Randomized
Figure 14.2.3.2	Plot of Paired Natriuresis	Randomized
Table 14.2.4.1	Summary of Furosemide Concentration and Ratio of Urinary Sodium to Urinary Furosemide	Randomized
Figure 14.2.4.2	Plot of Paired Furosemide Concentration and Ratio of Urinary Sodium to Urinary Furosemide	Randomized
Table 14.2.5	Summary of eGFR and Creatinine Levels	Randomized
Table 14.2.6	Summary of Renal and Urinary Biomarkers	Randomized
Table 14.2.7	Summary of Body Weight	Randomized
Table 14.2.8	Summary of Body Bio-Impedance	Randomized
Table 14.2.9	Summary of Ultrasound Indices of Congestion	Randomized
Table 14.2.10	Summary of Lung Ultrasound Indices of Pulmonary Congestion	Randomized
Table 14.2.11	Summary of Pulmonary B-lines	Randomized
Section 14.2 – Pharmacokinetic Data		
Table 14.2.12.1	Summary of Furosemide Plasma Concentrations	Randomized
Table 14.2.12.2	Summary of Furosemide Urine Recovery by Interval	Randomized

Table 14.2.12.3	Summary of Furosemide Urine Recovery	Randomized
Table 14.2.12.4	Summary of BMS-986231 and Metabolite Plasma Concentrations	Randomized
Table 14.2.12.5	Summary of BMS-986231 and Metabolite Urine Recovery by Interval	Randomized
Section 14.3 – Safety Data		
Table 14.3.1.1	Summary of Adverse Events	Safety
Table 14.3.1.2	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety
Table 14.3.1.3	Summary of Treatment Emergent Adverse Events by Relationship to Loestrin	Safety
Table 14.3.1.4	Summary of Treatment Emergent Adverse Events by Relationship to BMS-986231	Safety
Table 14.3.1.5	Summary of Treatment Emergent Adverse Events by Severity	Safety
Table 14.3.2	Listing of Deaths and Other Serious Adverse Events	Enrolled
Table 14.3.3	*Not part of TFL – Reserved for Narratives in CSR*	
Table 14.3.4	Listing of Abnormal Laboratory Values	Enrolled
Table 14.3.5	Summary of Safety Laboratory Results	Safety
Table 14.3.6	Summary of Vital Signs	Safety
Table 14.3.7	Summary of 12-Lead Electrocardiogram Results	Safety

List of End of Text Listings:	
Output	**Title**
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Listing 16.2.1.1	Subject Disposition
Listing 16.2.1.2	Eligibility Criteria
Section 16.2.2 – Protocol Deviations	
Listing 16.2.2	Important Protocol Deviations
Section 16.2.3 – Excluded Subjects	
Listing 16.2.3	Analysis Sets
Section 16.2.4 – Demographics and Baseline Characteristics	
Listing 16.2.4.1	Subject Demographics
Listing 16.2.4.2	Medical History
Listing 16.2.4.3	Childbearing Potential
Listing 16.2.4.4	Prior and Concomitant Medications
Section 16.2.5 - Compliance	
Listing 16.2.5.1	Study Drug Administration – BMS986231 or Placebo
Listing 16.2.5.2	Study Drug Administration – Furosemide
Section 16.2.6 – Response Data	
Listing 16.2.6.1.1	Urinary Output

Listing 16.2.6.1.2	Urinary Output - Differences
Listing 16.2.6.2.1	Excretion of FeNa and FeK
Listing 16.2.6.2.2	Fractional Excretion of FeNa and FeK - Differences
Listing 16.2.6.3.1	Natriuresis
Listing 16.2.6.3.2	Natriuresis - Differences
Listing 16.2.6.4.1	Furosemide Concentration and Ratio of Urinary Sodium to Urinary Furosemide
Listing 16.2.6.4.2	Furosemide Concentration and Ratio of Urinary Sodium to Urinary Furosemide - Differences
Listing 16.2.6.5.1	eGFR and Creatinine Levels
Listing 16.2.6.5.2	eGFR and Creatinine Levels – Differences
[redacted]	[redacted]
Listing 16.2.6.6.2	Renal and Urinary Biomarkers – Differences
Listing 16.2.6.7.1	Body Weight
Listing 16.2.6.7.2	Body Weight – Differences
Listing 16.2.6.8.1	Body Bio-Impedance
Listing 16.2.6.8.2	Body Bio-Impedance – Differences
Listing 16.2.6.9.1	Cardiac Ultrasound Indices of Congestion
Listing 16.2.6.9.2	Cardiac Ultrasound Indices of Congestion – Differences
Listing 16.2.6.10.1	Lung Ultrasound Indices of Pulmonary Congestion
Listing 16.2.6.10.2	Lung Ultrasound Indices of Pulmonary Congestion – Differences
Listing 16.2.6.11.1	Pulmonary B-lines
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Section 16.2.7 – Pharmacokinetic Data	
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Listing 16.2.7.2	Listing of Furosemide Urine Concentrations
Listing 16.2.7.3	Listing of Furosemide Urine Recovery
Listing 16.2.7.4	Listing of BMS-986231 and Metabolite Plasma Concentrations
Listing 16.2.7.5	Listing of BMS-986231 and Metabolite Urine Concentrations
Section 16.2.8 – Adverse Events Data	
Listing 16.2.8.1	Adverse Events
Listing 16.2.8.2	Adverse Events Resulting in Study Drug Discontinuation
Section 16.2.9 – Laboratory Data	
Listing 16.2.9.1	Clinical Laboratory Results – Chemistry
Listing 16.2.9.2	Clinical Laboratory Results – Hematology
Listing 16.2.9.3	Clinical Laboratory Results – Pregnancy Test
Section 16.2.10 Onward – Other Safety Data	
Listing 16.2.10.1	Vital Signs
Listing 16.2.10.2	Hypotension

Listing 16.2.11	12-Lead Electrocardiogram Results
Listing 16.2.12	Physical Examinations

Other Appendix Outputs:	
Output	**Title**
Appendix 16.1.9.2	Statistical Appendices

Appendix 6: Shells for Tables, Figures and Listings

Shells are provided in a separate document.

18.0 Document History

Version Date	Modified/Reviewed By	Brief Summary of Changes
13-Dec-2019	[redacted]	Created from EDSREP 009 T 01 G including agreements for the PRA/ BMS Phase I work.
20-Dec-2019		Implemented comments from internal review
22-Jan-2020		Implemented comments from internal and sponsor review