Clinical trial results:
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

Summary

EudraCT number	2018-000970-31
Trial protocol	GB
Global end of trial date	09 January 2020

Results information

Result version number	v1 (current)
This version publication date	24 January 2021
First version publication date	24 January 2021

Trial information

Trial identification

Sponsor protocol code	CV013-034

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 November 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 23
Worldwide total number of subjects	23
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	8
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

23 participants were randomized/assigned to treatment, and 23 initiated period 1 treatment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence 1

Arm description:

First received placebo (period 1), then received BMS-986231 (period 2) following washout. Each treatment administered 8 hours continuous IV infusion at the dose of 12 µg/kg/min, corresponding to an infusion rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide administered through a separate IV line, given slowly over 1 to 2 minutes.

Arm type	Experimental
Investigational medicinal product name	BMS-986231
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Dosed period 2

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Dosed period 1

Arm title	Sequence 2

Arm description:

First received BMS-986231 (period 1), then received placebo (period 2) following washout. Each treatment administered 8 hours continuous IV infusion at the dose of 12 µg/kg/min, corresponding to an infusion rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide administered through a separate IV line, given slowly over 1 to 2 minutes.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Dosed period 2

Investigational medicinal product name	BMS-986231
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Dosed period 1

Number of subjects in period 1	Sequence 1	Sequence 2
Started	12	11
Period 1 (P1) completion	12	11
Period 2 (P2) completion	11 [1]	10
Completed	12	10
Not completed	0	1
Adverse event, non-fatal	-	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 1 participant did not complete Period 2 but remained in the study, completing the study

Baseline characteristics

Reporting groups	
Reporting group title	Sequence 1
Reporting group description:	
First received placebo (period 1), then received BMS-986231 (period 2) following washout. Each treatment administered 8 hours continuous IV infusion at the dose of 12 µg/kg/min, corresponding to an infusion rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide administered through a separate IV line, given slowly over 1 to 2 minutes.	
Reporting group title	Sequence 2
Reporting group description:	
First received BMS-986231 (period 1), then received placebo (period 2) following washout. Each treatment administered 8 hours continuous IV infusion at the dose of 12 µg/kg/min, corresponding to an infusion rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide administered through a separate IV line, given slowly over 1 to 2 minutes.	

Reporting group values	Sequence 1	Sequence 2	Total
Number of subjects	12	11	23
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	6	2	8
>=65 years	6	9	15
Age Continuous Units: Years			
arithmetic mean	67.7	69.8	
standard deviation	± 8.19	± 8.23	-
Sex: Female, Male Units: Participants			
Female	1	1	2
Male	11	10	21
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	11	11	22
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	12	11	23
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Sequence 1

Reporting group description:

First received placebo (period 1), then received BMS-986231 (period 2) following washout. Each treatment administered 8 hours continuous IV infusion at the dose of 12 µg/kg/min, corresponding to an infusion rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide administered through a separate IV line, given slowly over 1 to 2 minutes.

Reporting group title	Sequence 2

Reporting group description:

First received BMS-986231 (period 1), then received placebo (period 2) following washout. Each treatment administered 8 hours continuous IV infusion at the dose of 12 µg/kg/min, corresponding to an infusion rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide administered through a separate IV line, given slowly over 1 to 2 minutes.

Subject analysis set title	BMS-986231
Subject analysis set type	Per protocol

Subject analysis set description:

BMS-986231 administered 8 hours continuous IV infusion at the dose of 12 µg/kg/min, corresponding to an infusion rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide administered through a separate IV line, given slowly over 1 to 2 minutes.

Subject analysis set title	Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

Placebo administered 8 hours continuous IV infusion of D5W administered at the flow rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide administered through a separate IV line, given slowly over 1 to 2 minutes.

Subject analysis set title	BMS-986231
Subject analysis set type	Intention-to-treat

Subject analysis set description:

BMS-986231 administered 8 hours continuous IV infusion at the dose of 12 µg/kg/min, corresponding to an infusion rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide administered through a separate IV line, given slowly over 1 to 2 minutes.

Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Placebo administered 8 hours continuous IV infusion of D5W administered at the flow rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide administered through a separate IV line, given slowly over 1 to 2 minutes.

Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Placebo administered 8 hours continuous IV infusion of D5W administered at the flow rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide administered through a separate IV line, given slowly over 1 to 2 minutes.

Subject analysis set title	BMS-986231
Subject analysis set type	Intention-to-treat

Subject analysis set description:

BMS-986231 administered 8 hours continuous IV infusion at the dose of 12 µg/kg/min, corresponding to an infusion rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide administered through a separate IV line, given slowly over 1 to 2 minutes.

Subject analysis set title	BMS-986231
Subject analysis set type	Per protocol

Subject analysis set description:

BMS-986231 administered 8 hours continuous IV infusion at the dose of 12 µg/kg/min, corresponding to an infusion rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide

administered through a separate IV line, given slowly over 1 to 2 minutes.

Subject analysis set title	Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

Placebo administered 8 hours continuous IV infusion of D5W administered at the flow rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide administered through a separate IV line, given slowly over 1 to 2 minutes.

Primary: 4-hour urinary output following intravenous administration of 40 mg furosemide to HFrEF participants receiving BMS-986231 infusion compared to placebo

End point title	4-hour urinary output following intravenous administration of 40 mg furosemide to HFrEF participants receiving BMS-986231 infusion compared to placebo

End point description:

The total volume of urinary output 4 hours after 40 mg furosemide bolus given to participants with HFrEF while on BMS-986231 compared to placebo: absolute difference in total volume and % change from placebo. Sequence 1: Placebo in period 1, drug in period 2 Sequence 2: Drug in period 1, placebo in period 2

End point type	Primary

End point timeframe:

4 hours

End point values	BMS-986231	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: mL				
arithmetic mean (standard deviation)				
Sequence 1	900.7 (± 366.56)	1603.3 (± 674.18)		
Sequence 2	1176.7 (± 386.21)	1345.4 (± 391.11)		
Total	1032.1 (± 392.74)	1480.5 (± 559.92)		

Statistical analyses

Statistical analysis title	Percent change of Drug vs placebo
Comparison groups	Placebo v BMS-986231
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0222
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-22.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.7
upper limit	-3.51

Statistical analysis title	Drug vs placebo
Comparison groups	BMS-986231 v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-448
Confidence interval	
level	95 %
sides	2-sided
lower limit	-714
upper limit	-183

Secondary: FeNa in participants with HFrEF while on BMS-986231 compared to placebo

End point title	FeNa in participants with HFrEF while on BMS-986231 compared to placebo

End point description:

Secondary efficacy analyses was performed using the randomized population. The FeNa, FeK, furosemide urinary and plasma concentration and the ratio of urinary sodium to urinary furosemide was 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. Fractional Excretion Na = ((Urine Sodium * Plasma Creatinine) / (Plasma Sodium * Urine Creatinine)) * 100

End point type	Secondary

End point timeframe:

Day 1, predose; 0-4 hours, 4-5 hours, 5-6 hours, 6-7 hours, 7-8 hours

End point values	BMS-986231	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	23		
Units: percent of filtered sodium				
arithmetic mean (standard deviation)				
Before start of infusion	0.5 (± 0.52)	0.6 (± 0.73)		
0-4 hours	0.6 (± 0.67)	0.7 (± 0.84)		
4-5 hours	4.6 (± 3.34)	5.4 (± 3.09)		
5-6 hours	5.0 (± 2.87)	7.0 (± 3.51)		
6-7 hours	3.3 (± 2.33)	4.7 (± 2.79)		

7-8 hours	1.7 (± 1.26)	3.3 (± 2.52)		

Statistical analyses

Statistical analysis title	Drug - placebo, 0-4 hours after furosemide
Comparison groups	BMS-986231 v Placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0163
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-4.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.63
upper limit	-0.876

Statistical analysis title	Percent change, 0-4 hours after furosemide
Comparison groups	BMS-986231 v Placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2018
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.8
upper limit	8.77

Statistical analysis title	Drug - placebo, 0-8 hours after start of infusion
Comparison groups	BMS-986231 v Placebo

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0526
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-3.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.27
upper limit	0.0446

Statistical analysis title	Percent change, 0-8 hours after start of infusion
Comparison groups	BMS-986231 v Placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2076
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-14.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.8
upper limit	9

Secondary: FeK in participants with HFrEF while on BMS-986231 compared to placebo

End point title	FeK in participants with HFrEF while on BMS-986231 compared to placebo

End point description:

Secondary efficacy analyses was performed using the randomized population. The FeNa, FeK, furosemide urinary and plasma concentration and the ratio of urinary sodium to urinary furosemide was 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. Fractional Excretion K = ((Urine Potassium * Plasma Creatinine) / (Plasma Potassium * Urine Creatinine)) * 100

End point type	Secondary

End point timeframe:

Day 1, predose; 0-4 hours, 4-5 hours, 5-6 hours, 6-7 hours, 7-8 hours

End point values	BMS-986231	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	23		
Units: percent of filtered potassium				
arithmetic mean (standard deviation)				
Before start of infusion	0.4 (± 0.16)	0.4 (± 0.17)		
0-4 hours	0.5 (± 0.20)	0.4 (± 0.17)		
4-5 hours	1.1 (± 0.67)	0.9 (± 0.46)		
5-6 hours	1.2 (± 0.54)	1.2 (± 0.52)		
6-7 hours	1.1 (± 0.42)	1.0 (± 0.35)		
7-8 hours	1.0 (± 0.32)	0.8 (± 0.32)		

Statistical analyses

Statistical analysis title	Drug - placebo, 0-4 hours after furosemide
Comparison groups	BMS-986231 v Placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1621
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	0.431
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.189
upper limit	1.05

Statistical analysis title	Percent change, 0-4 hours after furosemide
Comparison groups	BMS-986231 v Placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0338
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	32
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.72
upper limit	61.3

Statistical analysis title	Drug - placebo, 0-8 hours after start of infusion
Comparison groups	BMS-986231 v Placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.06
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	0.766
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0353
upper limit	1.57

Statistical analysis title	Percent change, 0-8 hours after start of infusion
Comparison groups	BMS-986231 v Placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.028
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	33.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.02
upper limit	63

Secondary: Furosemide urinary concentrations	
End point title	Furosemide urinary concentrations
End point description:	
Summary of urine recovery by interval, measured by amount excreted.	
End point type	Secondary
End point timeframe:	
Day 1, predose, 0-2 hours, 2-4 hours, 4-5 hours, 5-6 hours, 6-7 hours, 7-8 hours, 8-10 hours	

End point values	BMS-986231	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	23		
Units: mg				
arithmetic mean (standard deviation)				
Before start of infusion	0.2 (± 0.13)	0.2 (± 0.11)		
0-2 hours	0.1 (± 0.08)	0.1 (± 0.11)		
2-4 hours	0.3 (± 0.37)	0.1 (± 0.11)		
4-5 hours	7.9 (± 4.66)	8.2 (± 4.56)		
5-6 hours	4.3 (± 1.74)	3.7 (± 1.48)		
6-7 hours	2.8 (± 2.03)	2.7 (± 1.43)		
7-8 hours	2.0 (± 1.22)	1.7 (± 1.15)		
8-10 hours	1.7 (± 1.28)	1.6 (± 1.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Furosemide plasma concentrations

End point title	Furosemide plasma concentrations
End point description:	
Summary of plasma concentrations by interval.	
End point type	Secondary
End point timeframe:	
Day 1: 4, 5, 6, 8, 10 hours	

End point values	BMS-986231	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	23		
Units: ng/mL				
arithmetic mean (standard deviation)				
4 hours post-dose	1605 (± 5384)	63.6 (± 140.3)		
5 hours post-dose	2049 (± 593.0)	2145 (± 653.2)		
6 hours post-dose	1122 (± 437.6)	1146 (± 466.8)		
8 hours post-dose	426.8 (± 204.8)	476.6 (± 226.0)		
10 hours post-dose	345.6 (± 386.6)	244.3 (± 164.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ratio urinary sodium (Na) to urinary furosemide at 8 hours post-start

infusion

End point title	Ratio urinary sodium (Na) to urinary furosemide at 8 hours post-start infusion

End point description:

Summary of urinary concentrations 0-4 hours after furosemide Ratio = Cumulative Sodium Excretion / Cumulative Furosemide in Urine Note: 9999 represents NA (not applicable)

End point type	Secondary

End point timeframe:

0-4 hours after furosemide

End point values	BMS-986231	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: Ratio of Urinary Na:Urinary furosemide				
arithmetic mean (standard deviation)				
Drug and placebo	6.1 (± 3.18)	10.1 (± 4.74)		
Difference between drug and placebo	-4.0 (± 4.74)	9999 (± 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with clinically relevant hypotension

End point title	Number of participants with clinically relevant hypotension

End point description:

Clinically relevant hypotension is defined as systolic blood pressure (SBP) < 90 mmHg or symptomatic hypotension during infusion

End point type	Secondary

End point timeframe:

up to 8 hours

End point values	BMS-986231	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	23		
Units: Number of participants	4	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with an Adverse Event (AE)

End point title	Number of participants with an Adverse Event (AE)

End point description:

Clinically relevant hypotension is defined as systolic blood pressure (SBP) < 90 mmHg or symptomatic hypotension during infusion

End point type	Secondary

End point timeframe:

up to 8 days

End point values	BMS-986231	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	23		
Units: Number of participants	8	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with an Abnormal Clinical Laboratory Value

End point title	Number of participants with an Abnormal Clinical Laboratory Value

End point description:

Number of participants who experienced an in-study abnormal clinical laboratory event under the category of Hematology, Chemistry or Urinalysis.

End point type	Secondary

End point timeframe:

from first dose to 30 days post-last dose (ca. 5-8 weeks)

End point values	BMS-986231	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	23		
Units: Number of participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Vital Signs - blood pressure

End point title	Change from baseline in Vital Signs - blood pressure

End point description:

The change in baseline for vital signs was reported for each arm.

End point type	Secondary

End point timeframe:

Day 1, 8 hours post-dose (end of infusion)

End point values	BMS-986231	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	22		
Units: mmHg				
arithmetic mean (standard deviation)				
diastolic blood pressure	-14.5 (± 9.99)	-0.6 (± 10.46)		
systolic blood pressure	-28.4 (± 15.60)	-4.9 (± 14.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Vital Signs - heart rate

End point title	Change from baseline in Vital Signs - heart rate

End point description:

The change in baseline for vital signs was reported for each arm.

End point type	Secondary

End point timeframe:

Day 1, 8 hours post-dose (end of infusion)

End point values	Placebo	BMS-986231		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: beats/min				
arithmetic mean (standard deviation)	-0.1 (± 8.08)	0.5 (± 10.40)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Vital Signs - oxygen saturation

End point title	Change from baseline in Vital Signs - oxygen saturation

End point description:

The change in baseline for vital signs was reported for each arm.

End point type	Secondary

End point timeframe:

Day 1, 8 hours post-dose (end of infusion)

End point values	BMS-986231	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	22		
Units: oxygen saturation percentage				
arithmetic mean (standard deviation)	-1.0 (± 1.82)	0.0 (± 1.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Electrocardiograms (ECGs) - mean heart rate

End point title	Change from baseline in Electrocardiograms (ECGs) - mean heart rate

End point description:

The change in baseline for ECGs was reported for each arm.

End point type	Secondary

End point timeframe:

Day 1, 8 hours post-dose (end of infusion)

End point values	Placebo	BMS-986231		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	23		
Units: beats/min				
arithmetic mean (standard deviation)	1.6 (± 7.61)	0.9 (± 7.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Electrocardiograms (ECGs) - PR, QRS Duration, QT, QTcF Intervals

End point title	Change from baseline in Electrocardiograms (ECGs) - PR, QRS Duration, QT, QTcF Intervals

End point description:

The change in baseline for ECGs was reported for each arm.

End point type	Secondary

End point timeframe:

Day 1, 8 hours post-dose (end of infusion)

End point values	Placebo	BMS-986231		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	23		
Units: msec				
arithmetic mean (standard deviation)				
PR Interval, Aggregate	-2.8 (± 12.17)	2.0 (± 24.21)		
QRS Duration, Aggregate	2.2 (± 21.46)	-0.9 (± 25.91)		
QT Interval, Aggregate	-7.9 (± 16.95)	-9.1 (± 27.88)		
QTcF Interval, Aggregate	-5.1 (± 16.74)	-11.2 (± 26.90)		

Statistical analyses

No statistical analyses for this end point

Secondary: Telemetry

End point title	Telemetry
End point description:	
Telemetry data not collected.	
End point type	Secondary
End point timeframe:	
Day 1, 8 hours post-dose	

End point values	BMS-986231	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[1]	0[2]		
Units: Number of Participants				

Notes:

[1] - Analysis population is 0, data not collected

[2] - Analysis population is 0, data not collected

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Physical Examination - body weight

End point title	Change from baseline in Physical Examination - body weight
End point description:	
The change in baseline for physical examinations was reported for each arm.	
End point type	Secondary
End point timeframe:	
Day 1, 8 hours post-dose (end of infusion)	

End point values	BMS-986231	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	19		
Units: kg				
arithmetic mean (standard deviation)	0.2 (± 0.77)	-0.5 (± 0.72)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the time of signing the consent up to 30 days of discontinuation of dosing

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects were intravenously administered with a single infusion of BMS-986231 matching placebo at a dose of 20 milliliter per hour for 8 hours.

Reporting group title	BMS-986231

Reporting group description:

Subjects were intravenously administered with a single infusion of BMS-986231 at a dose of 12 microgram per kilogram per minute for 8 hours (20 milliliter per hour).

Serious adverse events	Placebo	BMS-986231	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 23 (8.70%)	1 / 23 (4.35%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dyspnoea			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	BMS-986231	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 23 (13.04%)	6 / 23 (26.09%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 23 (0.00%)	3 / 23 (13.04%)	
occurrences (all)	0	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 23 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	1 / 23 (4.35%)	3 / 23 (13.04%)	
occurrences (all)	1	3	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	2 / 23 (8.70%)	0 / 23 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2019	Update of the address for BMS Update of the Medical Monitor Update of Appendix 3 to clarify the definition of adverse event to be used in the study Correction position vital signs in Table 1 In addition, minor editorial corrections were included
14 March 2019	Allowance of more flexibility to the investigators regarding withholding diuretics and fluid intake and emphasizing that the target population should be patients with stable chronic heart failure with reduced ejection fraction (HFrEF) without signs of decompensation. Clarification that if the end of infusion occurs prior to 8 hours after start of infusion (H8), the end of infusion should be considered an early discontinuation. Minor editorial and administrative changes.
15 April 2019	Changes to Section 5.1 Inclusion Criteria, to allow participants with lower levels of baseline natriuretic peptides and higher baseline estimated glomerular filtration rate (eGFR). Minor editorial or administrative changes or corrections of typographical errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported