Clinical trial results:
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

Summary

EudraCT number	2016-003586-26
Trial protocol	GB NL
Global end of trial date	10 May 2019

Results information

Result version number	v1 (current)
This version publication date	22 May 2020
First version publication date	22 May 2020

Trial information

Trial identification

Sponsor protocol code	CV013-020

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	07 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 May 2019
Global end of trial reached?	Yes
Global end of trial date	10 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effects of BMS-986231 on the left ventricular (LV) systolic function by stroke volume index (SVI) assessed by echocardiography compared to placebo

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	30 November 2017
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: 34
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Japan: 2
Worldwide total number of subjects	49
EEA total number of subjects	45

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)	22
From 65 to 84 years	27

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

49 participants assigned to treatment and 45 treated. Reasons not treated: 2 re-randomized; 1 randomized in error, screen failure; 1 no longer met study criteria.

Note: Study designed for all participants to enter all 3 arms (reassignment of arms occurs every period change).

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

Placebo-matching treatment. Note: Periods are separated by washouts.

Arm type	Placebo
Investigational medicinal product name	Placebo-matching treatment
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mL/H for 10 min 10 mL/H for 10 min 20 mL/H for the rest of the 5-hour infusion. Placebo is a solution of 5% dextrose (D5W)

Arm title	BMS-986231

Arm description:

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. Note: Periods are separated by washouts.

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

Dosage and administration details:

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)

Arm title	Nitroglycerin (NTG)

Arm description:

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 Note: Periods are separated by washouts.

Arm type	Experimental

Investigational medicinal product name	Nitroglycerin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

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)

Number of subjects in period 1	Placebo	BMS-986231	Nitroglycerin (NTG)
Started	40	42	44
Completed	40	40	43
Not completed	0	2	1
Hypotension	-	2	-
Acute bradycardia and hypotension	-	-	1

Period 2

Period 2 title	Period 1
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo-matching treatment. Note: Periods are separated by washouts.

Arm type	Placebo
Investigational medicinal product name	Placebo-matching treatment
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mL/H for 10 min 10 mL/H for 10 min 20 mL/H for the rest of the 5-hour infusion. Placebo is a solution of 5% dextrose (D5W)

Arm title	BMS-986231

Arm description:

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. Note: Periods are separated by washouts.

Arm type	Experimental

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

Dosage and administration details:

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)

Arm title	Nitroglycerin (NTG)

Arm description:

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 Note: Periods are separated by washouts.

Arm type	Experimental
Investigational medicinal product name	Nitroglycerin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

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)

Number of subjects in period 2	Placebo	BMS-986231	Nitroglycerin (NTG)
Started	15	17	13
Completed	15	16	12
Not completed	0	1	1
stop due to hypotension, cont. period 2	-	1	-
Acute bradycardia and hypotension	-	-	1

Period 3

Period 3 title	Following Period 1, prior to Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes

Arm title	Placebo
Arm description:	
Placebo-matching treatment. Note: Periods are separated by washouts.	
Arm type	Placebo
Investigational medicinal product name	Placebo-matching treatment
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
5 mL/H for 10 min 10 mL/H for 10 min 20 mL/H for the rest of the 5-hour infusion. Placebo is a solution of 5% dextrose (D5W)	
Arm title	BMS-986231
Arm description:	
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. Note: Periods are separated by washouts.	
Arm type	Experimental
Investigational medicinal product name	BMS-986231
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
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)	
Arm title	Nitroglycerin (NTG)
Arm description:	
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 Note: Periods are separated by washouts.	
Arm type	Experimental
Investigational medicinal product name	Nitroglycerin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
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)	

Number of subjects in period 3	Placebo	BMS-986231	Nitroglycerin (NTG)
Started	15	16	12
Participant return	15	17	12
Completed	14	16	11
Not completed	1	1	1
withdrew consent due to personal reasons	-	1	-
Lost to follow-up	-	-	1
withdrew due to acute cholecystitis	1	-	-

Joined	0	1	0
stopped Pd. 1 treatment but returned for Pd. 2	-	1	-

Period 4

Period 4 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo-matching treatment. Note: Periods are separated by washouts.

Arm type	Placebo
Investigational medicinal product name	Placebo-matching treatment
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mL/H for 10 min 10 mL/H for 10 min 20 mL/H for the rest of the 5-hour infusion. Placebo is a solution of 5% dextrose (D5W)

Arm title	BMS-986231

Arm description:

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. Note: Periods are separated by washouts.

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

Dosage and administration details:

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)

Arm title	Nitroglycerin (NTG)

Arm description:

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 Note: Periods are separated by washouts.

Arm type	Experimental

Investigational medicinal product name	Nitroglycerin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

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)

Number of subjects in period 4	Placebo	BMS-986231	Nitroglycerin (NTG)
Started	13	13	15
Completed	13	12	15
Not completed	0	1	0
Hypotension	-	1	-

Period 5

Period 5 title	Following Period 2, prior to Period 3
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo-matching treatment. Note: Periods are separated by washouts.

Arm type	Placebo
Investigational medicinal product name	Placebo-matching treatment
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mL/H for 10 min 10 mL/H for 10 min 20 mL/H for the rest of the 5-hour infusion. Placebo is a solution of 5% dextrose (D5W)

Arm title	BMS-986231

Arm description:

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. Note: Periods are separated by washouts.

Arm type	Experimental

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

Dosage and administration details:

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)

Arm title	Nitroglycerin (NTG)

Arm description:

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 Note: Periods are separated by washouts.

Arm type	Experimental
Investigational medicinal product name	Nitroglycerin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

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)

Number of subjects in period 5	Placebo	BMS-986231	Nitroglycerin (NTG)
Started	13	12	15
participant re-sequence	13	13	15
Completed	13	12	15
Not completed	0	1	0
Adverse event, non-fatal	-	1	-
Joined	0	1	0
participants reassigned treatment for Period 3	-	1	-

Period 6

Period 6 title	Period 3
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes

Arm title	Placebo

Arm description:

Placebo-matching treatment. Note: Periods are separated by washouts.

Arm type	Placebo
Investigational medicinal product name	Placebo-matching treatment
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mL/H for 10 min 10 mL/H for 10 min 20 mL/H for the rest of the 5-hour infusion. Placebo is a solution of 5% dextrose (D5W)

Arm title	BMS-986231

Arm description:

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. Note: Periods are separated by washouts.

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

Dosage and administration details:

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)

Arm title	Nitroglycerin (NTG)

Arm description:

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 Note: Periods are separated by washouts.

Arm type	Experimental
Investigational medicinal product name	Nitroglycerin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

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)

Number of subjects in period 6[1]	Placebo	BMS-986231	Nitroglycerin (NTG)
Started	12	12	15
Completed	12	12	15

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Note: Study designed for all participants to enter all 3 arms (reassignment of arms occurs every period change)

Baseline characteristics

Reporting groups[1]	
Reporting group title	Overall baseline
Reporting group description:	
Inclusive of all treatments, all periods	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: 49 participants were assigned to treatment and 45 treated. Note: Study designed for all participants to enter all 3 arms (reassignment of arms occurs every period change)

Reporting group values	Overall baseline	Total	
Number of subjects	45	45	
Age Categorical Units: Participants			
<=18 years	0	0	
Between 18 and 65 years	20	20	
>=65 years	25	25	
Age Continuous Units: Years			
arithmetic mean	63.7		
standard deviation	± 12.35	-	
Sex: Female, Male Units: Participants			
Female	8	8	
Male	37	37	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	3	3	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	40	40	
More than one race	0	0	
Unknown or Not Reported	1	1	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	2	2	
Unknown or Not Reported	43	43	

Subject analysis sets	
Subject analysis set title	Overall participants
Subject analysis set type	Safety analysis
Subject analysis set description:	
Inclusive of all treatments, all periods	

Reporting group values	Overall participants		
Number of subjects	45		
Age Categorical Units: Participants			
<=18 years	0		
Between 18 and 65 years	20		
>=65 years	25		
Age Continuous Units: Years			
arithmetic mean	63.7		
standard deviation	± 12.35		
Sex: Female, Male Units: Participants			
Female	8		
Male	37		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	3		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	40		
More than one race	0		
Unknown or Not Reported	1		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	2		
Unknown or Not Reported	43		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo-matching treatment. Note: Periods are separated by washouts.	
Reporting group title	BMS-986231
Reporting group description:	
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. Note: Periods are separated by washouts.	
Reporting group title	Nitroglycerin (NTG)
Reporting group description:	
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 Note: Periods are separated by washouts.	
Reporting group title	Placebo
Reporting group description:	
Placebo-matching treatment. Note: Periods are separated by washouts.	
Reporting group title	BMS-986231
Reporting group description:	
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. Note: Periods are separated by washouts.	
Reporting group title	Nitroglycerin (NTG)
Reporting group description:	
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 Note: Periods are separated by washouts.	
Reporting group title	Placebo
Reporting group description:	
Placebo-matching treatment. Note: Periods are separated by washouts.	
Reporting group title	BMS-986231
Reporting group description:	
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. Note: Periods are separated by washouts.	
Reporting group title	Nitroglycerin (NTG)
Reporting group description:	
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 Note: Periods are separated by washouts.	
Reporting group title	Placebo
Reporting group description:	
Placebo-matching treatment. Note: Periods are separated by washouts.	
Reporting group title	BMS-986231
Reporting group description:	
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. Note: Periods are separated by washouts.	
Reporting group title	Nitroglycerin (NTG)
Reporting group description:	
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 Note: Periods are separated by washouts.	
Reporting group title	Placebo
Reporting group description:	
Placebo-matching treatment. Note: Periods are separated by washouts.	
Reporting group title	BMS-986231
Reporting group description:	
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. Note: Periods are separated by washouts.

Reporting group title	Nitroglycerin (NTG)

Reporting group description:

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 Note: Periods are separated by washouts.

Reporting group title	Placebo

Reporting group description:

Placebo-matching treatment. Note: Periods are separated by washouts.

Reporting group title	BMS-986231

Reporting group description:

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. Note: Periods are separated by washouts.

Reporting group title	Nitroglycerin (NTG)

Reporting group description:

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 Note: Periods are separated by washouts.

Subject analysis set title	Overall participants
Subject analysis set type	Safety analysis

Subject analysis set description:

Inclusive of all treatments, all periods

Primary: Mean Stroke Volume Index (SVI) derived from the velocity time integral at the left ventricular outflow tract (LVOT VTI) at the end of the 5-hour infusion of BMS-986231, versus placebo

End point title	Mean Stroke Volume Index (SVI) derived from the velocity time integral at the left ventricular outflow tract (LVOT VTI) at the end of the 5-hour infusion of BMS-986231, versus placebo[1]

End point description:

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

End point type	Primary

End point timeframe:

at the end of the 5-hour infusion

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is in regards to placebo and drug arms only

End point values	Placebo	BMS-986231		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	37		
Units: mL/m^2				
arithmetic mean (standard deviation)				
SVI, placebo and drug	29.545 (± 7.0243)	28.721 (± 9.0174)		

Statistical analyses

Statistical analysis title	Mean SVI (placebo and drug)
Comparison groups	BMS-986231 v Placebo

Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027
Method	Kenward-Roger degree of freedom
Parameter estimate	Mean difference (net)
Point estimate	-2.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.0432
upper limit	-0.257
Variability estimate	Standard error of the mean
Dispersion value	0.9242

Secondary: Mean SVI derived from LVOT VTI at the end of the 5-hour infusion of BMS-986231, versus NTG

End point title	Mean SVI derived from LVOT VTI at the end of the 5-hour infusion of BMS-986231, versus NTG[2]

End point description:

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

End point type	Secondary

End point timeframe:

at the end of the 5-hour infusion

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is in regards to NTG and drug arms only

End point values	BMS-986231	Nitroglycerin (NTG)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	41		
Units: mL/m^2				
arithmetic mean (standard deviation)				
SVI, drug and NTG	28.721 (± 9.0174)	27.811 (± 7.9712)		

Statistical analyses

Statistical analysis title	Mean SVI (drug and NTG)
Comparison groups	BMS-986231 v Nitroglycerin (NTG)

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.846
Method	Kenward-Roger degree of freedom
Parameter estimate	Mean difference (net)
Point estimate	0.193
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8176
upper limit	2.2042
Variability estimate	Standard error of the mean
Dispersion value	0.9832

Secondary: Mean LVEF, computed by Simpson’s method at the end of the 5-hour infusion of BMS-986231, versus placebo and NTG

End point title	Mean LVEF, computed by Simpson’s method at the end of the 5-hour infusion of BMS-986231, versus placebo and NTG

End point description:

Evaluate the effects of BMS-986231 on selected other left ventricular systolic and diastolic indices compared to placebo and NTG: LV ejection fraction

End point type	Secondary

End point timeframe:

at the end of the 5-hour infusion

End point values	Placebo	BMS-986231	Nitroglycerin (NTG)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	36	42	
Units: Percentage of blood pumped from the LV				
arithmetic mean (standard deviation)				
LVEF	31.9 (± 7.15)	32.8 (± 8.24)	33.5 (± 7.33)	

Statistical analyses

Statistical analysis title	Mean LVEF (placebo and drug)
Comparison groups	Placebo v BMS-986231

Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.177
Method	Kenward-Roger degree of freedom
Parameter estimate	Mean difference (net)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	3.19
Variability estimate	Standard error of the mean
Dispersion value	0.93

Statistical analysis title	Mean LVEF (drug and NTG)
Comparison groups	BMS-986231 v Nitroglycerin (NTG)
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.839
Method	Kenward-Roger degree of freedom
Parameter estimate	Mean difference (net)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.08
upper limit	0.88
Variability estimate	Standard error of the mean
Dispersion value	0.48

Secondary: Mean cardiac power index at the end of the 5-hour infusion of BMS-986231, versus placebo and NTG

End point title	Mean cardiac power index at the end of the 5-hour infusion of BMS-986231, versus placebo and NTG

End point description:

Evaluate the effects of BMS-986231 on selected other left ventricular systolic and diastolic indices compared to placebo and NTG: Mean LV power index

End point type	Secondary

End point timeframe:

at the end of the 5-hour infusion

End point values	Placebo	BMS-986231	Nitroglycerin (NTG)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	35	36	39	
Units: watts per square meter (W/m^2)				
arithmetic mean (standard deviation)				
cardiac power index	0.4122 (± 0.14404)	0.3427 (± 0.10463)	0.3568 (± 0.09184)	

Statistical analyses

Statistical analysis title	Mean cardiac power index (placebo and drug)
Comparison groups	Placebo v BMS-986231
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Kenward-Roger degree of freedom
Parameter estimate	Mean difference (net)
Point estimate	-0.0977
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16634
upper limit	-0.02915
Variability estimate	Standard error of the mean
Dispersion value	0.03308

Statistical analysis title	Mean cardiac power index (drug and NTG)
Comparison groups	BMS-986231 v Nitroglycerin (NTG)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.103
Method	Kenward-Roger degree of freedom
Parameter estimate	Mean difference (net)
Point estimate	-0.0371
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08243
upper limit	0.00814
Variability estimate	Standard error of the mean
Dispersion value	0.02194

Secondary: Mean Diastolic indices: E/A, annular e' velocity, and E/e' ratio at the end of the 5-hour infusion of BMS-986231, versus placebo and NTG

End point title	Mean Diastolic indices: E/A, annular e' velocity, and E/e' ratio at the end of the 5-hour infusion of BMS-986231, versus placebo and NTG

End point description:

Evaluate the effects of BMS-986231 on selected other left ventricular systolic and diastolic indices compared to placebo and NTG: Diastolic function

End point type	Secondary

End point timeframe:

at the end of the 5-hour infusion

End point values	Placebo	BMS-986231	Nitroglycerin (NTG)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	34	40	
Units: Percentage				
arithmetic mean (standard deviation)				
E/A ratio	0.80 (± 0.278)	0.73 (± 0.270)	0.71 (± 0.310)	
annular e' velocity ratio	9.42 (± 4.102)	7.00 (± 2.464)	7.81 (± 2.652)	
E/e' ratio	7.18 (± 2.467)	8.07 (± 2.333)	7.18 (± 2.143)	

Statistical analyses

Statistical analysis title	Mean E/A ratio (placebo and drug)

Statistical analysis description:

E/A ratio

Comparison groups	Placebo v BMS-986231
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Kenward-Roger degree of freedom
Parameter estimate	Mean difference (net)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.205
upper limit	-0.051
Variability estimate	Standard error of the mean
Dispersion value	0.037

Statistical analysis title	Mean E/A ratio (drug and NTG)

Statistical analysis description: E/A ratio	
Comparison groups	BMS-986231 v Nitroglycerin (NTG)
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.904
Method	Kenward-Roger degree of freedom
Parameter estimate	Mean difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.051
upper limit	0.057
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	Diastolic Indices E/e ratio (placebo and drug)
Statistical analysis description: Diastolic Indices E/e ratio	
Comparison groups	Placebo v BMS-986231
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Kenward-Roger degree of freedom
Parameter estimate	Mean difference (net)
Point estimate	-1.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.763
upper limit	-0.549
Variability estimate	Standard error of the mean
Dispersion value	0.527

Statistical analysis title	Diastolic Indices E/e ratio (drug and NTG)
Statistical analysis description: Diastolic Indices E/e ratio	
Comparison groups	BMS-986231 v Nitroglycerin (NTG)

Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.503
Method	Kenward-Roger degree of freedom
Parameter estimate	Mean difference (net)
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.085
upper limit	0.55
Variability estimate	Standard error of the mean
Dispersion value	0.392

Statistical analysis title	Mean E/e' ratio (placebo and drug)
Statistical analysis description:	
E/e' ratio	
Comparison groups	Placebo v BMS-986231
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.994
Method	Kenward-Roger degree of freedom
Parameter estimate	Mean difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.827
upper limit	0.82
Variability estimate	Standard error of the mean
Dispersion value	0.398

Statistical analysis title	Mean E/e' ratio (drug and NTG)
Statistical analysis description:	
E/e' ratio	
Comparison groups	BMS-986231 v Nitroglycerin (NTG)
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.073
Method	Kenward-Roger degree of freedom
Parameter estimate	Mean difference (net)
Point estimate	0.48

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.049
upper limit	1.013
Variability estimate	Standard error of the mean
Dispersion value	0.258

Secondary: Mean LV global longitudinal strain, computed using STE at the end of the 5-hour infusion of BMS-986231, versus placebo and NTG

End point title	Mean LV global longitudinal strain, computed using STE at the end of the 5-hour infusion of BMS-986231, versus placebo and NTG

End point description:

Evaluate the effects of BMS-986231 on selected other left ventricular systolic and diastolic indices compared to placebo and NTG: LV global longitudinal strain

End point type	Secondary

End point timeframe:

at the end of the 5-hour infusion

End point values	Placebo	BMS-986231	Nitroglycerin (NTG)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	36	43	
Units: Percentage of blood pumped from the LV				
arithmetic mean (standard deviation)				
LV global longitudinal strain	-11.98 (± 2.860)	-11.94 (± 3.458)	-11.36 (± 3.067)	

Statistical analyses

Statistical analysis title	LV global longitudinal strain (placebo and drug)
Comparison groups	Placebo v BMS-986231
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.705
Method	Kenward-Roger degree of freedom
Parameter estimate	Mean difference (net)
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	0.976

Variability estimate	Standard error of the mean
Dispersion value	0.4

Statistical analysis title	LV global longitudinal strain (drug and NTG)
Comparison groups	BMS-986231 v Nitroglycerin (NTG)
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.105
Method	Kenward-Roger degree of freedom
Parameter estimate	Mean difference (net)
Point estimate	-0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.504
upper limit	0.151
Variability estimate	Standard error of the mean
Dispersion value	0.404

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) were collected from the date of informed consent up to 30 days post-infusion of the last period. Non-serious AEs were collected from the start of the study drug infusion. until 24 hours post-infusion.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects were intravenously administered with a single infusion of placebo (5% dextrose) at a rate of 5 milliliters per hour (mL/hr) for 10 min; 10 mL/hr for 10 min and 20 mL/hr for the rest of the 5-hour. Subjects received treatment on Day 1 during Period 1, 2 and 3 followed by wash-out from Day 2 up to Day 28 during Period 1 and 2.

Reporting group title	Nitroglycerin

Reporting group description:

Nitroglycerin: Subjects were intravenously administered with a single infusion of Nitroglycerin at a dose of 20 µg/min for 10 min (5 mL/hr); 40 µg/min for 10 min (10 mL/hr) and 80 µg/min for the rest of the 5-hour infusion (20 mL/hr). Subjects received treatment on Day 1 during Period 1, 2 and 3 followed by wash-out from Day 2 up to Day 28 during Period 1 and 2.

Reporting group title	BMS-986231

Reporting group description:

Subjects were intravenously administered with a single infusion of BMS-986231 at a dose of 3 microgram per kilogram per minute (µg/kg/min) for 10 min (5 mL/hr); 6 µg/kg/min for 10 min (10 mL/hr) and 12 µg/kg/min for the rest of the 5-hour infusion (20 mL/hr). Subjects received treatment on Day 1 during Period 1, 2 and 3 followed by wash-out from Day 2 up to Day 28 during Period 1 and 2.

Serious adverse events	Placebo	Nitroglycerin	BMS-986231
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)	0 / 44 (0.00%)	0 / 42 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Placebo	Nitroglycerin	BMS-986231
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 40 (5.00%)	10 / 44 (22.73%)	12 / 42 (28.57%)
Vascular disorders			

Hypotension subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	3 / 44 (6.82%) 3	5 / 42 (11.90%) 5
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	7 / 44 (15.91%) 7	10 / 42 (23.81%) 10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 June 2017	Inserted additional text into Section 8.1: 'Discontinuation from Study Treatment' to allow the patient to be part of the IP continuation discussion when confirmed pregnant.
01 September 2017	Clarification of allowable contraceptives for WOCBP, addition of chronic nitrates use criteria, clarification of IP preparation, handling and storage
17 July 2018	To modify the inclusion/exclusion criteria to allow the true representation of stable heart failure participants into the study, shorten the washout period, allow use of contrast echocardiography to improve endocardial definition, as needed, and clarification on the procedures for participants prior to day 1.
05 September 2018	Incorporating Administrative Letters 03 and 04 content that was not included in Revised Protocol 03: - To clarify the origin of Nitroglycerin supplied by BMS. - Correct minor typographical errors identified throughout the protocol.
24 January 2019	Clarified the wording the Appendix 3 to harmonize AE definitions in BMS clinical studies. Clarified the enrollment numbers under study drug.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported