Clinical trial results:
A randomized parallel-group, placebo-controlled, double-blind, multicenter, dose-finding Phase II trial exploring the pharmacodynamic effects, safety and tolerability, and pharmacokinetics of four dose regimens of the oral sGC stimulator vericiguat over 12 weeks in patients with worsening heart failure and reduced ejection fraction (HFrEF) - Soluble guanylate Cyclase stimulator in heart failure patients with REDUCED EF (SOCRATES-REDUCED)

Summary

EudraCT number	2013-002287-11
Trial protocol	CZ IT AT BE SE DK DE ES NL HU BG GR
Global end of trial date	09 June 2015

Results information

Result version number	v3 (current)
This version publication date	03 April 2022
First version publication date	25 June 2016
Version creation reason	• Correction of full data set updates on data presentation

Trial information

Trial identification

Sponsor protocol code	BAY1021189/15371

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01951625
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368,Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	29 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the study was to find the optimal dose of the oral soluble guanylate cyclase (sGC) stimulator vericiguat for Phase III that can be given in addition to standard therapy for heart failure with reduced ejection fraction (EF) (HFrEF) by characterizing the safety, tolerability, pharmacodynamic effects, and pharmacokinetics (PK), and detecting a significant dose-response relationship in the primary endpoint change in N-terminal pro-brain natriuretic peptide (NT-ProBNP) at 12 weeks in subjects with worsening chronic heart failure with reduced ejection fraction (HFrEF).

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects and/or their legally authorized representative. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 November 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	Sweden: 15
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Taiwan: 24
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	United States: 25
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Austria: 17
Country: Number of subjects enrolled	Belgium: 23
Country: Number of subjects enrolled	Bulgaria: 41
Country: Number of subjects enrolled	Canada: 4

Country: Number of subjects enrolled	Czech Republic: 16
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	Greece: 17
Country: Number of subjects enrolled	Hungary: 24
Country: Number of subjects enrolled	Israel: 42
Country: Number of subjects enrolled	Italy: 40
Country: Number of subjects enrolled	Japan: 30
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Poland: 32
Country: Number of subjects enrolled	Singapore: 21
Worldwide total number of subjects	456
EEA total number of subjects	300

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)	172
From 65 to 84 years	256
85 years and over	28

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 144 centers in 24 countries between 29 November 2013 (first subject first visit) and 09 June 2015 (last subject last visit).

Pre-assignment

Screening details:

Of the total 632 subjects enrolled, 176 were screen failure and 456 were randomized. After randomization 1 did not receive study drug, and of the 455 treated subjects 348 completed both Treatment and Follow Up periods. All Arms in FU period were mutually exclusive, this question below is ticked No because of database validation rule constraints.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received placebo matched to vericiguat (BAY1021189) orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo matched to vericiguat (BAY1021189) orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.

Arm title	BAY1021189 1.25 milligram (mg)

Arm description:

Subjects received vericiguat (BAY1021189) 1.25 mg orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.

Arm type	Experimental
Investigational medicinal product name	Vericiguat
Investigational medicinal product code	BAY1021189
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received single oral dose of Vericiguat tablet (BAY1021189) 1.25 mg once daily for 12 weeks with sham titrations on 14 and 28 days.

Arm title	BAY1021189 2.5 mg

Arm description:

Subjects received vericiguat (BAY1021189) 2.5 mg orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.

Arm type	Experimental

Investigational medicinal product name	Vericiguat
Investigational medicinal product code	BAY1021189
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received vericiguat (BAY1021189) 2.5 mg orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.

Arm title	BAY1021189 from 2.5 to 5 mg

Arm description:

Subjects received vericiguat (BAY1021189) for 12 weeks, starting on 2.5 mg once daily with potential up-titration to 5 mg once daily after 14 or 28 days. Sham titration included on Day 28.

Arm type	Experimental
Investigational medicinal product name	Vericiguat
Investigational medicinal product code	BAY1021189
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received vericiguat (BAY1021189) for 12 weeks, starting on 2.5mg once daily with potential up-titration to 5 mg once daily after 14 or 28 days. Sham titration included on Day 28.

Arm title	BAY1021189 from 2.5 to 10 mg

Arm description:

Subjects received vericiguat (BAY1021189) for 12 weeks, starting on 2.5 mg once daily with potential up-titration to 5 mg once daily after 14 days, and up-titration to 10 mg once daily after 28 days.

Arm type	Experimental
Investigational medicinal product name	Vericiguat
Investigational medicinal product code	BAY1021189
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received vericiguat (BAY1021189) for 12 weeks, starting on 2.5 mg once daily with potential up-titration to 5 mg once daily after 14 days, and up-titration to 10 mg once daily after 28 days.

Number of subjects in period 1	Placebo	BAY1021189 1.25 milligram (mg)	BAY1021189 2.5 mg
Started	92	91	91
Completed	73	70	76
Not completed	19	21	15
Adverse event, serious fatal	3	2	2
Consent withdrawn by subject	5	2	1
Physician decision	-	-	-
Adverse event, non-fatal	7	10	9
Protocol driven decision point	-	5	-
Lost to follow-up	1	-	-
Non compliance with study drug	1	2	2

Protocol deviation	2	-	1

Number of subjects in period 1	BAY1021189 from 2.5 to 5 mg	BAY1021189 from 2.5 to 10 mg
Started	91	91
Completed	69	74
Not completed	22	17
Adverse event, serious fatal	1	2
Consent withdrawn by subject	7	3
Physician decision	-	1
Adverse event, non-fatal	8	8
Protocol driven decision point	2	1
Lost to follow-up	1	-
Non compliance with study drug	-	-
Protocol deviation	3	2

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

Arms	
Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

Subjects received placebo matched to vericiguat (BAY1021189) orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo matched to vericiguat (BAY1021189) orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.

Arm title	BAY1021189 1.25 milligram (mg)

Arm description:

Subjects received vericiguat (BAY1021189) 1.25 mg orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.

Arm type	Experimental

Investigational medicinal product name	Vericiguat
Investigational medicinal product code	BAY1021189
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received single oral dose of Vericiguat tablet (BAY1021189) 1.25 mg once daily for 12 weeks with sham titrations on 14 and 28 days.

Arm title	BAY1021189 2.5 mg

Arm description:

Subjects received vericiguat (BAY1021189) 2.5 mg orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.

Arm type	Experimental
Investigational medicinal product name	Vericiguat
Investigational medicinal product code	BAY1021189
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received vericiguat (BAY1021189) 2.5 mg orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.

Arm title	BAY1021189 from 2.5 to 5 mg

Arm description:

Subjects received vericiguat (BAY1021189) for 12 weeks, starting on 2.5 mg once daily with potential up-titration to 5 mg once daily after 14 or 28 days. Sham titration included on Day 28.

Arm type	Experimental
Investigational medicinal product name	Vericiguat
Investigational medicinal product code	BAY1021189
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received vericiguat (BAY1021189) for 12 weeks, starting on 2.5mg once daily with potential up-titration to 5 mg once daily after 14 or 28 days. Sham titration included on Day 28.

Arm title	BAY1021189 from 2.5 to 10 mg

Arm description:

Subjects received vericiguat (BAY1021189) for 12 weeks, starting on 2.5 mg once daily with potential up-titration to 5 mg once daily after 14 days, and up-titration to 10 mg once daily after 28 days.

Arm type	Experimental
Investigational medicinal product name	Vericiguat
Investigational medicinal product code	BAY1021189
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received vericiguat (BAY1021189) for 12 weeks, starting on 2.5 mg once daily with potential up-titration to 5 mg once daily after 14 days, and up-titration to 10 mg once daily after 28 days.

Number of subjects in period 2	Placebo	BAY1021189 1.25 milligram (mg)	BAY1021189 2.5 mg
Started	87	88	88
Completed	79	79	84
Not completed	8	9	4
Adverse event, serious fatal	1	3	2
Consent withdrawn by subject	4	1	-
Logistical difficulties	1	2	-
Adverse event, non-fatal	-	3	2
Non-compliance with study drug	1	-	-
Lost to follow-up	1	-	-

Number of subjects in period 2	BAY1021189 from 2.5 to 5 mg	BAY1021189 from 2.5 to 10 mg
Started	87	88
Completed	76	78
Not completed	11	10
Adverse event, serious fatal	2	1
Consent withdrawn by subject	5	3
Logistical difficulties	-	-
Adverse event, non-fatal	3	5
Non-compliance with study drug	-	-
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to vericiguat (BAY1021189) orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.	
Reporting group title	BAY1021189 1.25 milligram (mg)
Reporting group description:	
Subjects received vericiguat (BAY1021189) 1.25 mg orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.	
Reporting group title	BAY1021189 2.5 mg
Reporting group description:	
Subjects received vericiguat (BAY1021189) 2.5 mg orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.	
Reporting group title	BAY1021189 from 2.5 to 5 mg
Reporting group description:	
Subjects received vericiguat (BAY1021189) for 12 weeks, starting on 2.5 mg once daily with potential up-titration to 5 mg once daily after 14 or 28 days. Sham titration included on Day 28.	
Reporting group title	BAY1021189 from 2.5 to 10 mg
Reporting group description:	
Subjects received vericiguat (BAY1021189) for 12 weeks, starting on 2.5 mg once daily with potential up-titration to 5 mg once daily after 14 days, and up-titration to 10 mg once daily after 28 days.	

Reporting group values	Placebo	BAY1021189 1.25 milligram (mg)	BAY1021189 2.5 mg
Number of subjects	92	91	91
Age categorical Units: Subjects			
<65	38	38	30
65-75	26	19	37
>=75	28	34	24
Age continuous Units: years			
arithmetic mean	67	67.6	67.6
standard deviation	± 13.1	± 12.9	± 11.5
Gender categorical Units: Subjects			
Female	19	21	19
Male	73	70	72

Reporting group values	BAY1021189 from 2.5 to 5 mg	BAY1021189 from 2.5 to 10 mg	Total
Number of subjects	91	91	456
Age categorical Units: Subjects			
<65	38	28	172
65-75	32	34	148
>=75	21	29	136

Age continuous Units: years			
arithmetic mean	66.7	68.9	
standard deviation	± 11.6	± 12.4	-
Gender categorical Units: Subjects			
Female	17	14	90
Male	74	77	366

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to vericiguat (BAY1021189) orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.	
Reporting group title	BAY1021189 1.25 milligram (mg)
Reporting group description:	
Subjects received vericiguat (BAY1021189) 1.25 mg orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.	
Reporting group title	BAY1021189 2.5 mg
Reporting group description:	
Subjects received vericiguat (BAY1021189) 2.5 mg orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.	
Reporting group title	BAY1021189 from 2.5 to 5 mg
Reporting group description:	
Subjects received vericiguat (BAY1021189) for 12 weeks, starting on 2.5 mg once daily with potential up-titration to 5 mg once daily after 14 or 28 days. Sham titration included on Day 28.	
Reporting group title	BAY1021189 from 2.5 to 10 mg
Reporting group description:	
Subjects received vericiguat (BAY1021189) for 12 weeks, starting on 2.5 mg once daily with potential up-titration to 5 mg once daily after 14 days, and up-titration to 10 mg once daily after 28 days.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to vericiguat (BAY1021189) orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.	
Reporting group title	BAY1021189 1.25 milligram (mg)
Reporting group description:	
Subjects received vericiguat (BAY1021189) 1.25 mg orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.	
Reporting group title	BAY1021189 2.5 mg
Reporting group description:	
Subjects received vericiguat (BAY1021189) 2.5 mg orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.	
Reporting group title	BAY1021189 from 2.5 to 5 mg
Reporting group description:	
Subjects received vericiguat (BAY1021189) for 12 weeks, starting on 2.5 mg once daily with potential up-titration to 5 mg once daily after 14 or 28 days. Sham titration included on Day 28.	
Reporting group title	BAY1021189 from 2.5 to 10 mg
Reporting group description:	
Subjects received vericiguat (BAY1021189) for 12 weeks, starting on 2.5 mg once daily with potential up-titration to 5 mg once daily after 14 days, and up-titration to 10 mg once daily after 28 days.	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS (N=456) included all subjects randomized to treatment and was used to display baseline characteristics and efficacy analyses.	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
SAF (N=455) included all subjects from FAS who received at least 1 dose of study drug and was used to display baseline characteristics and safety analyses.	
Subject analysis set title	Per protocol set (PPS)

Subject analysis set type	Per protocol

Subject analysis set description:

PPS (N=351) included subjects who were randomized to treatment and had a valid measurement of NT-proBNP at baseline and at Week 12 and showed no major protocol deviations. The PPS was the primary analysis set for the primary efficacy analysis and was used for further efficacy analyses and baseline characteristics.

Subject analysis set title	Pooled 2.5 mg up to 10 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled 2.5 mg up to 10 mg: (N= 213) The three highest dose arms (BAY1021189 2.5 mg, 2.5-5 mg, and 2.5-10 mg) were pooled and used for the primary analysis of the primary endpoint. This Pooled 2.5 mg up to 10 mg group is serving as "Reporting Group" for primary analysis instead of Sub-group analysis, however Sub-group analysis is chosen as analysis set type because there is no proper option provided in database.

Primary: Change From Baseline in Log-Transformed N-Terminal Pro-Brain Natriuretic Peptide (NTproBNP) to Week 12

End point title	Change From Baseline in Log-Transformed N-Terminal Pro-Brain Natriuretic Peptide (NTproBNP) to Week 12

End point description:

Log-Transformed N-Terminal Pro-Brain Natriuretic Peptide (NTproBNP) is a circulating plasma biomarker of cardiovascular function and prognosis in heart failure.

End point type	Primary

End point timeframe:

Baseline, Week 12

End point values	Placebo	BAY1021189 1.25 milligram (mg)	BAY1021189 2.5 mg	BAY1021189 from 2.5 to 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69[1]	69[2]	73[3]	67[4]
Units: log-transformed picograms per milliliter				
arithmetic mean (standard deviation)	-0.28 (± 0.8197)	-0.265 (± 0.7658)	-0.32 (± 0.7799)	-0.353 (± 0.8404)

Notes:

[1] - PPS

[2] - PPS

[3] - PPS

[4] - PPS

End point values	BAY1021189 from 2.5 to 10 mg	Pooled 2.5 mg up to 10 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	73[5]	213		
Units: log-transformed picograms per milliliter				
arithmetic mean (standard deviation)	-0.529 (± 0.9475)	-0.402 (± 0.8603)		

Notes:

[5] - PPS

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

For the primary analysis, the three highest active treatment groups (BAY1021189 2.5mg, BAY1021189 2.5 to 5mg, BAY1021189 2.5 to 10mg) were pooled and compared to the assigned placebo treatment group with a one-sided two-sample t-test at the significance level of 5 percent (%). Results are reported including 90% confidence intervals (CI) for the difference of means. The difference between the pooled treatment group and the placebo group is difference of means on the log scale.

Comparison groups	Placebo v Pooled 2.5 mg up to 10 mg
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1506
Method	t-test, 1-sided
Parameter estimate	Log-Scale mean difference
Point estimate	-0.122
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.32
upper limit	0.07

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

In case of a significant result in the primary analysis of the primary endpoint, pairwise comparisons to Placebo were performed in a hierarchical manner (from BAY1021189 from 2.5 to 10mg dose arm to BAY1021189 1.25mg dose arm). In accordance with the specification in the protocol these secondary analyses are considered exploratory only, since the primary analyses were not significant.

Comparison groups	Placebo v BAY1021189 from 2.5 to 10 mg
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0483
Method	t-test, 1-sided
Parameter estimate	Log-Scale mean difference
Point estimate	-0.2494
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.5
upper limit	0

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

In case of a significant result in the primary analysis of the primary endpoint, pairwise comparisons to Placebo were performed in a hierarchical manner (from BAY1021189 from 2.5 to 10mg dose arm to BAY1021189 1.25mg dose arm). In accordance with the specification in the protocol these secondary analyses are considered exploratory only, since the primary analyses were not significant.

Comparison groups	Placebo v BAY1021189 from 2.5 to 5 mg

Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3042
Method	t-test, 1-sided
Parameter estimate	Log-Scale mean difference
Point estimate	-0.0731
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.31
upper limit	0.16

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

In case of a significant result in the primary analysis of the primary endpoint, pairwise comparisons to Placebo were performed in a hierarchical manner (from BAY1021189 from 2.5 to 10mg dose arm to BAY1021189 1.25mg dose arm). In accordance with the specification in the protocol these secondary analyses are considered exploratory only, since the primary analyses were not significant.

Comparison groups	Placebo v BAY1021189 2.5 mg
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3841
Method	t-test, 1-sided
Parameter estimate	Log-Scale mean difference
Point estimate	-0.0396
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.26
upper limit	0.18

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

In case of a significant result in the primary analysis of the primary endpoint, pairwise comparisons to Placebo were performed in a hierarchical manner (from BAY1021189 from 2.5 to 10mg dose arm to BAY1021189 1.25mg dose arm). In accordance with the specification in the protocol these secondary analyses are considered exploratory only, since the primary analyses were not significant.

Comparison groups	Placebo v BAY1021189 1.25 milligram (mg)
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5444
Method	t-test, 1-sided
Parameter estimate	Log-Scale mean difference
Point estimate	0.0151

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.21
upper limit	0.24

Other pre-specified: Changes in Heart Function as Measured by Echocardiography, Left Ventricular Ejection Fraction (LVEF), Left Ventricular End-Diastolic Volume (LVEDV), and Left Ventricular End-Systolic Volume (LVESV) From Baseline to Week 12

End point title	Changes in Heart Function as Measured by Echocardiography, Left Ventricular Ejection Fraction (LVEF), Left Ventricular End-Diastolic Volume (LVEDV), and Left Ventricular End-Systolic Volume (LVESV) From Baseline to Week 12

End point description:

Left Ventricular End-Diastolic Volume (LVEDV) and Left ventricular end-systolic volume (LVESV) are measured echocardiography parameter. These are acquired during a non-invasive echocardiography examination. The left ventricular ejection fraction work index (LVEF) is a calculated echocardiography parameter. LVEF is derived from the directly measured parameters left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV). Formula: LVEF = 100*(LVEDV - LVESV)/LVEDV. Here, n = subjects evaluable for specified category for each arm, respectively.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 12

End point values	Placebo	BAY1021189 1.25 milligram (mg)	BAY1021189 2.5 mg	BAY1021189 from 2.5 to 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	92[6]	91[7]	91[8]	91[9]
Units: % for LVEF; ml for LVEDV/LVESV				
arithmetic mean (standard deviation)				
Change in LVEF (%): (n=70,65,69,63,71)	1.515 (± 4.736)	2.84 (± 3.635)	2.741 (± 4.371)	2.07 (± 4.808)
Change in LVEDV (milliliter): (n=70,65,69,63,70)	-7.259 (± 40.676)	-5.525 (± 34.75)	-9.632 (± 35.081)	-17.093 (± 53.307)
Change in LVESV (milliliter): (n=70,65,69,63,71)	-6.83 (± 32.407)	-8.585 (± 27.385)	-10.935 (± 27.146)	-15.485 (± 43.191)

Notes:

[6] - Evaluable subjects in FAS

[7] - Evaluable subjects in FAS

[8] - Evaluable subjects in FAS

[9] - Evaluable subjects in FAS

End point values	BAY1021189 from 2.5 to 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	91[10]			
Units: % for LVEF; ml for LVEDV/LVESV				
arithmetic mean (standard deviation)				

Change in LVEF (%): (n=70,65,69,63,71)	3.682 (± 6.19)			
Change in LVEDV (milliliter): (n=70,65,69,63,70)	-7.324 (± 31.896)			
Change in LVESV (milliliter): (n=70,65,69,63,71)	-11.017 (± 26.525)			

Notes:

[10] - Evaluable subjects in FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Systolic and Diastolic Blood Pressure to Week 12

End point title	Change From Baseline in Systolic and Diastolic Blood Pressure to Week 12

End point description:

Blood pressure was measured after at least 10 minutes resting in a sitting position (3 measurements taken approximately 2 minutes apart).The changes in blood pressure were recorded and the mean of the three measurements was analyzed. Here, n = subjects evaluable for specified category for each arm, respectively.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 12

End point values	Placebo	BAY1021189 1.25 milligram (mg)	BAY1021189 2.5 mg	BAY1021189 from 2.5 to 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	92[11]	91[12]	90[13]	91[14]
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
Change in SBP: (n= 73, 70, 75, 69, 74)	-5.142 (± 12.829)	-4.033 (± 13.3)	-3.733 (± 16.509)	-3.043 (± 15.934)
Change in DBP: (n= 73, 70, 75, 69, 74)	-4.173 (± 8.6)	-0.486 (± 9.298)	-2.938 (± 11.101)	-1.338 (± 9.528)

Notes:

[11] - SAF

[12] - SAF

[13] - SAF

[14] - SAF

End point values	BAY1021189 from 2.5 to 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	91[15]			
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
Change in SBP: (n= 73, 70, 75, 69, 74)	-5.64 (± 15.509)			

Change in DBP: (n= 73, 70, 75, 69, 74)	-4.045 (± 10.604)			

Notes:

[15] - SAF

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Heart rate to Week 12

End point title	Change From Baseline in Heart rate to Week 12

End point description:

Heart rate was measured after 10 minutes resting in a sitting position (3 measurements taken approximatly 2 minutes apart). The changes in heart rate were recorded and the mean of the three measurements was analyzed. Here, n = subjects evaluable for specified category for each arm, respectively.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 12

End point values	Placebo	BAY1021189 1.25 milligram (mg)	BAY1021189 2.5 mg	BAY1021189 from 2.5 to 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	92[16]	91[17]	90[18]	91[19]
Units: Beats per minute				
arithmetic mean (standard deviation)				
Change at Week 12 (n= 73, 70, 75, 69, 74)	-0.562 (± 12.897)	-0.352 (± 10.153)	-1.556 (± 10.2)	-0.99 (± 11.295)

Notes:

[16] - SAF

[17] - SAF

[18] - SAF

[19] - SAF

End point values	BAY1021189 from 2.5 to 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	91[20]			
Units: Beats per minute				
arithmetic mean (standard deviation)				
Change at Week 12 (n= 73, 70, 75, 69, 74)	0.545 (± 10.636)			

Notes:

[20] - SAF

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Clinical Events (Heart Failure [HF] Hospitalization and Cardio-Vascular [CV] Mortality)

End point title	Number of Subjects With Clinical Events (Heart Failure [HF] Hospitalization and Cardio-Vascular [CV] Mortality)

End point description:

Clinical events (heart failure and mortality) were analyzed as CV death, and HF hospitalization at specified time points.

End point type	Other pre-specified

End point timeframe:

Baseline until 16 weeks including 12 week treatment period and 4 week follow-up period

End point values	Placebo	BAY1021189 1.25 milligram (mg)	BAY1021189 2.5 mg	BAY1021189 from 2.5 to 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	92[21]	91[22]	91[23]	91[24]
Units: subjects				
HF hospitalizations	21	18	20	10
CV death	6	5	4	2

Notes:

[21] - FAS

[22] - FAS

[23] - FAS

[24] - FAS

End point values	BAY1021189 from 2.5 to 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	91[25]			
Units: subjects				
HF hospitalizations	9			
CV death	4			

Notes:

[25] - FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Implantable Cardioverter Defibrillators Cardiac Resynchronization Therapy With Defibrillation (ICD/CRT-D) Therapy

End point title	Number of Subjects With Implantable Cardioverter Defibrillators Cardiac Resynchronization Therapy With Defibrillation (ICD/CRT-D) Therapy

End point description:

ICD / CRT with defibrillation therapy (CRT-D) included previous appropriate interventions such as shocks or anti-tachycardic pacing (ATP) when diagnostic of sustained ventricular tachycardias in pre defined

rapid zone.

End point type	Other pre-specified

End point timeframe:

Baseline upto 16 weeks

End point values	Placebo	BAY1021189 1.25 milligram (mg)	BAY1021189 2.5 mg	BAY1021189 from 2.5 to 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[26]	0[27]	0[28]	0[29]
Units: subjects				

Notes:

[26] - No analysis was performed for this end point.

[27] - No analysis was performed for this end point.

[28] - No analysis was performed for this end point.

[29] - No analysis was performed for this end point.

End point values	BAY1021189 from 2.5 to 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	0[30]			
Units: subjects				

Notes:

[30] - No analysis was performed for this end point.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Treatment-Emergent Adverse Events

End point title	Number of Subjects With Treatment-Emergent Adverse Events

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly; and another medically important serious event as judged by the investigator. AEs are considered to be treatment-emergent if they have started or worsened after first application of study drug up to 5 days after end of treatment with study drug.

End point type	Other pre-specified

End point timeframe:

From the start of study treatment upto 5 days after the last dose of study drug

End point values	Placebo	BAY1021189 1.25 milligram (mg)	BAY1021189 2.5 mg	BAY1021189 from 2.5 to 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	92[31]	91[32]	90[33]	91[34]
Units: Number of subjects	66	60	62	62

Notes:

[31] - SAF

[32] - SAF

[33] - SAF

[34] - SAF

End point values	BAY1021189 from 2.5 to 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	91[35]			
Units: Number of subjects	56			

Notes:

[35] - SAF

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in biomarkers from baseline to week 12: Osteopontin (ng/mL)

End point title	Change in biomarkers from baseline to week 12: Osteopontin (ng/mL)

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline, Week 12

End point values	Placebo	BAY1021189 1.25 milligram (mg)	BAY1021189 2.5 mg	BAY1021189 from 2.5 to 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73[36]	69[37]	73[38]	65[39]
Units: nanogram(s)/milliliter (ng/mL)				
arithmetic mean (standard deviation)	2.79 (± 42.049)	3.812 (± 39.248)	3.266 (± 52.957)	8.485 (± 41.97)

Notes:

[36] - Evaluable subjects in FAS

[37] - Evaluable subjects in FAS

[38] - Evaluable subjects in FAS

[39] - Evaluable subjects in FAS

End point values	BAY1021189 from 2.5 to 10 mg			

Subject group type	Reporting group			
Number of subjects analysed	71[40]			
Units: nanogram(s)/milliliter (ng/mL)				
arithmetic mean (standard deviation)	3.709 (± 36.048)			

Notes:

[40] - Evaluable subjects in FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in biomarkers from baseline to week 12: TIMP-4 (pg/mL)

End point title	Change in biomarkers from baseline to week 12: TIMP-4 (pg/mL)

End point description:

TIMP-4: tissue inhibitor of matrix metalloproteinases 4

End point type	Other pre-specified

End point timeframe:

Baseline, Week 12

End point values	Placebo	BAY1021189 1.25 milligram (mg)	BAY1021189 2.5 mg	BAY1021189 from 2.5 to 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73[41]	69[42]	72[43]	67[44]
Units: picogram(s)/millilitre (pg/mL)				
arithmetic mean (standard deviation)	451.889 (± 1392.03)	1128.635 (± 1949.351)	643.626 (± 1441.954)	876.584 (± 1559.768)

Notes:

[41] - Evaluable subjects in FAS

[42] - Evaluable subjects in FAS

[43] - Evaluable subjects in FAS

[44] - Evaluable subjects in FAS

End point values	BAY1021189 from 2.5 to 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	72[45]			
Units: picogram(s)/millilitre (pg/mL)				
arithmetic mean (standard deviation)	397.603 (± 1420.223)			

Notes:

[45] - Evaluable subjects in FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in biomarkers from baseline to week 12: cGMP (pmol/mL)

End point title	Change in biomarkers from baseline to week 12: cGMP (pmol/mL)

End point description:

cGMP: cyclic guanosine monophosphate

End point type	Other pre-specified

End point timeframe:

Baseline, Week 12

End point values	Placebo	BAY1021189 1.25 milligram (mg)	BAY1021189 2.5 mg	BAY1021189 from 2.5 to 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73[46]	69[47]	73[48]	66[49]
Units: picomole(s)/milliliter (pmol/mL)				
arithmetic mean (standard deviation)	78.874 (± 143.321)	79.767 (± 123.031)	92.352 (± 121.477)	80.888 (± 114.09)

Notes:

[46] - Evaluable subjects in FAS

[47] - Evaluable subjects in FAS

[48] - Evaluable subjects in FAS

[49] - Evaluable subjects in FAS

End point values	BAY1021189 from 2.5 to 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	71[50]			
Units: picomole(s)/milliliter (pmol/mL)				
arithmetic mean (standard deviation)	63.563 (± 127.448)			

Notes:

[50] - Evaluable subjects in FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in biomarkers from baseline to week 12: PIIINP (mcg/L)

End point title	Change in biomarkers from baseline to week 12: PIIINP (mcg/L)

End point description:

PIIINP: pro-collagen III N-terminal peptide

End point type	Other pre-specified

End point timeframe:

Baseline, Week 12

End point values	Placebo	BAY1021189 1.25 milligram (mg)	BAY1021189 2.5 mg	BAY1021189 from 2.5 to 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70[51]	69[52]	72[53]	67[54]
Units: microgram(s)/liter (mcg/L)				
arithmetic mean (standard deviation)	-0.701 (± 7.246)	0.092 (± 3.958)	0.106 (± 5.145)	-0.71 (± 3.774)

Notes:

[51] - Evaluable subjects in FAS

[52] - Evaluable subjects in FAS

[53] - Evaluable subjects in FAS

[54] - Evaluable subjects in FAS

End point values	BAY1021189 from 2.5 to 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	73[55]			
Units: microgram(s)/liter (mcg/L)				
arithmetic mean (standard deviation)	-0.321 (± 4.452)			

Notes:

[55] - Evaluable subjects in FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in biomarkers from baseline to week 12: GDF-15 (pg/mL)

End point title	Change in biomarkers from baseline to week 12: GDF-15 (pg/mL)
End point description: GDF-15: growth differentiation factor 15	
End point type	Other pre-specified
End point timeframe: Baseline, Week 12	

End point values	Placebo	BAY1021189 1.25 milligram (mg)	BAY1021189 2.5 mg	BAY1021189 from 2.5 to 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73[56]	69[57]	73[58]	66[59]
Units: pg/mL				
arithmetic mean (standard deviation)	429.432 (± 3212.229)	496.456 (± 3132.738)	285.472 (± 2837.237)	468.369 (± 1786.062)

Notes:
[56] - Evaluable subjects in FAS
[57] - Evaluable subjects in FAS
[58] - Evaluable subjects in FAS
[59] - Evaluable subjects in FAS

End point values	BAY1021189 from 2.5 to 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	71[60]			
Units: pg/mL				
arithmetic mean (standard deviation)	244.63 (± 2906.763)			

Notes:
[60] - Evaluable subjects in FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in biomarkers from baseline to week 12: ST2 (pg/mL)

End point title	Change in biomarkers from baseline to week 12: ST2 (pg/mL)
End point description: ST2: suppression of tumorigenicity 2	
End point type	Other pre-specified
End point timeframe: Baseline, Week 12	

End point values	Placebo	BAY1021189 1.25 milligram (mg)	BAY1021189 2.5 mg	BAY1021189 from 2.5 to 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73[61]	69[62]	72[63]	67[64]
Units: pg/mL				
arithmetic mean (standard deviation)	9457.677 (± 54702.45)	1623.869 (± 25086.72)	-1217.77 (± 35166.41)	6933.941 (± 20747.71)

Notes:
[61] - Evaluable subjects in FAS
[62] - Evaluable subjects in FAS
[63] - Evaluable subjects in FAS
[64] - Evaluable subjects in FAS

End point values	BAY1021189 from 2.5 to 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	72[65]			
Units: pg/mL				
arithmetic mean (standard deviation)	3681.668 (± 32293.77)			

Notes:
[65] - Evaluable subjects in FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in biomarkers from baseline to week 12: Gal-3 (µg/mL)

End point title	Change in biomarkers from baseline to week 12: Gal-3 (µg/mL)

End point description:
Gal-3: Galectin-3

End point type	Other pre-specified

End point timeframe:
Baseline, Week 12

End point values	Placebo	BAY1021189 1.25 milligram (mg)	BAY1021189 2.5 mg	BAY1021189 from 2.5 to 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72[66]	68[67]	73[68]	64[69]
Units: mcg/L				
arithmetic mean (standard deviation)	0.802 (± 13.818)	0.233 (± 6.208)	-0.287 (± 3.729)	0.064 (± 5.64)

Notes:
[66] - Evaluable subjects in FAS
[67] - Evaluable subjects in FAS
[68] - Evaluable subjects in FAS
[69] - Evaluable subjects in FAS

End point values	BAY1021189 from 2.5 to 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	71[70]			
Units: mcg/L				
arithmetic mean (standard deviation)	-0.38 (± 4.551)			

Notes:
[70] - Evaluable subjects in FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent AEs were collected after first application of study medication up to 5 calendar days after end of treatment with study medication.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received placebo matched to vericiguat (BAY1021189) orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.

Reporting group title	BAY1021189 1.25 milligram (mg)

Reporting group description:

Subjects received vericiguat (BAY1021189) 1.25 mg orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.

Reporting group title	BAY1021189 2.5 mg

Reporting group description:

Subjects received vericiguat (BAY1021189) 2.5 mg orally once daily for 12 weeks. Sham titrations included on Days 14 and 28.

Reporting group title	BAY1021189 from 2.5 to 5 mg

Reporting group description:

Subjects received vericiguat (BAY1021189) for 12 weeks, starting on 2.5mg once daily with potential up-titration to 5 mg once daily after 14 or 28 days. Sham titration included on Day 28.

Reporting group title	BAY1021189 from 2.5 to 10 mg

Reporting group description:

Subjects received vericiguat (BAY1021189) for 12 weeks, starting on 2.5mg once daily with potential up-titration to 5 mg once daily after 14 days, and up-titration to 10 mg once daily after 28 days.

Serious adverse events	Placebo	BAY1021189 1.25 milligram (mg)	BAY1021189 2.5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 92 (32.61%)	26 / 91 (28.57%)	26 / 90 (28.89%)
number of deaths (all causes)	6	6	5
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal haemangioma			

subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Catheter placement			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Multi-organ failure			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Dyspnoea			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary congestion			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Transplant evaluation			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 92 (2.17%)	2 / 91 (2.20%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Incision site haemorrhage			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	8 / 92 (8.70%)	13 / 91 (14.29%)	10 / 90 (11.11%)
occurrences causally related to treatment / all	1 / 14	0 / 14	0 / 11
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 0
Cardiac failure acute			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	5 / 92 (5.43%)	2 / 91 (2.20%)	5 / 90 (5.56%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 92 (1.09%)	2 / 91 (2.20%)	3 / 90 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			

subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 92 (1.09%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute left ventricular failure			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicobrachial syndrome			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			

subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 92 (1.09%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			

subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mechanical ileus			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated umbilical hernia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash pruritic			

subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	3 / 92 (3.26%)	4 / 91 (4.40%)	2 / 90 (2.22%)
occurrences causally related to treatment / all	1 / 3	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 92 (1.09%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal sepsis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			

subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	2 / 90 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	BAY1021189 from 2.5 to 5 mg	BAY1021189 from 2.5 to 10 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 91 (21.98%)	25 / 91 (27.47%)	
number of deaths (all causes)	3	4	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemangioma			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	1 / 91 (1.10%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			

subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Catheter placement			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 91 (1.10%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 91 (1.10%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sudden death			
subjects affected / exposed	1 / 91 (1.10%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
General physical health deterioration			
subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	1 / 91 (1.10%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 91 (1.10%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 91 (1.10%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary congestion			
subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 91 (1.10%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Transplant evaluation			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site haemorrhage			
subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			

subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 91 (0.00%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 91 (3.30%)	3 / 91 (3.30%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute			
subjects affected / exposed	1 / 91 (1.10%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	3 / 91 (3.30%)	4 / 91 (4.40%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	2 / 91 (2.20%)	3 / 91 (3.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 91 (1.10%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			

subjects affected / exposed	1 / 91 (1.10%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	1 / 91 (1.10%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicobrachial syndrome			
subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 91 (1.10%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	1 / 91 (1.10%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated umbilical hernia			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash pruritic			
subjects affected / exposed	0 / 91 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 91 (1.10%)	3 / 91 (3.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 91 (1.10%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 91 (2.20%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract infection			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			

subjects affected / exposed	0 / 91 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 91 (1.10%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	BAY1021189 1.25 milligram (mg)	BAY1021189 2.5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 92 (26.09%)	25 / 91 (27.47%)	20 / 90 (22.22%)
Vascular disorders			
Hypotension			
subjects affected / exposed	6 / 92 (6.52%)	5 / 91 (5.49%)	5 / 90 (5.56%)
occurrences (all)	6	5	6
Cardiac disorders			
Cardiac failure chronic			
subjects affected / exposed	4 / 92 (4.35%)	1 / 91 (1.10%)	5 / 90 (5.56%)
occurrences (all)	5	1	5
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 92 (5.43%)	3 / 91 (3.30%)	2 / 90 (2.22%)
occurrences (all)	6	3	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 92 (3.26%)	0 / 91 (0.00%)	2 / 90 (2.22%)
occurrences (all)	3	0	2
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 92 (2.17%)	5 / 91 (5.49%)	1 / 90 (1.11%)
occurrences (all)	2	6	1
Dyspepsia			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences (all)	0	1	0

Nausea			
subjects affected / exposed	3 / 92 (3.26%)	5 / 91 (5.49%)	3 / 90 (3.33%)
occurrences (all)	4	6	3
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	5 / 92 (5.43%)	1 / 91 (1.10%)	3 / 90 (3.33%)
occurrences (all)	5	1	3
Cough			
subjects affected / exposed	6 / 92 (6.52%)	8 / 91 (8.79%)	4 / 90 (4.44%)
occurrences (all)	7	8	4
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	2 / 90 (2.22%)
occurrences (all)	1	0	2
Hypokalaemia			
subjects affected / exposed	3 / 92 (3.26%)	5 / 91 (5.49%)	2 / 90 (2.22%)
occurrences (all)	3	5	2

Non-serious adverse events	BAY1021189 from 2.5 to 5 mg	BAY1021189 from 2.5 to 10 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 91 (25.27%)	28 / 91 (30.77%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 91 (4.40%)	14 / 91 (15.38%)	
occurrences (all)	4	17	
Cardiac disorders			
Cardiac failure chronic			
subjects affected / exposed	2 / 91 (2.20%)	0 / 91 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 91 (2.20%)	5 / 91 (5.49%)	
occurrences (all)	2	5	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 91 (5.49%)	2 / 91 (2.20%)	
occurrences (all)	5	2	

Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 91 (1.10%)	0 / 91 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	1 / 91 (1.10%)	5 / 91 (5.49%)	
occurrences (all)	1	7	
Nausea			
subjects affected / exposed	1 / 91 (1.10%)	1 / 91 (1.10%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 91 (2.20%)	4 / 91 (4.40%)	
occurrences (all)	3	4	
Cough			
subjects affected / exposed	4 / 91 (4.40%)	4 / 91 (4.40%)	
occurrences (all)	4	4	
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	5 / 91 (5.49%)	0 / 91 (0.00%)	
occurrences (all)	5	0	
Hypokalaemia			
subjects affected / exposed	2 / 91 (2.20%)	5 / 91 (5.49%)	
occurrences (all)	2	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 July 2013	The purpose of this global amendment was to implement clarifications (primarily in exclusion criteria and study procedures): Exclusion criteria were clarified to facilitate enrollment of appropriate subjects, to prevent over-interpretation and exclusion of eligible subjects, and to minimize protocol deviations: -The exclusion criterion "IV inotropes at any time after hospitalization" was revised to "IV inotropes at any time between hospitalization and randomization" to clarify that there was no prohibition of inotropes after randomization (if HF re-hospitalization occurred). -The exclusion criterion "…valvular heart disease with severe aortic or mitral regurgitation…"was revised to "…valvular heart disease with severe aortic or primary mitral regurgitation…" to clarify that secondary (functional) mitral regurgitation was not excluded. -The exclusion criterion " ..or CABG within 60 days prior to randomization; or indication for percutaneous coronary intervention (PCI) or CABG" was revised to "…or CABG within 60 days prior to randomization. Current indication for PCI or CABG (at time of randomization)" to clarify that no 60-day lag time was required after elective PCI. -Excluded BMI was changed from >40 kg/m^2 to >45 kg/m^2 to adapt the upper range of eligible BMI to the observed clinical characteristics at participating sites in order to recruit a population that was representative, including those with high BMI. The additional mandatory criterion of NT-ProBNP/BNP ensured the presence of HF in those subjects with very high BMI. Study procedures were clarified to minimize protocol deviations. The protocol was clarified in that there was only one committee, the Clinical Events Committee (CEC), and only one manual, the CEC manual, to adjudicate events. IV vasodilators were included as indicative of worsening chronic heart failure (WCHF) to be consistent with the CEC manual. The protocol was clarified in that HR was also measured during echocardiography.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Endpoints of "Change in 'health-related quality of life', 'Composite Congestion Score', 'NYHA function class', and 'background heart failure therapies' were assessed as exploratory. "Incidence of atrial fibrillation" is reported in AE summary.

Notes: