Clinical trial results:
A randomized parallel-group, placebo-controlled, double-blind, multi-center dose finding phase II trial exploring the pharmacodynamic effects, safety and tolerability, and pharmacokinetics of four dose regimens of the oral sGC stimulator BAY 1021189 over 12 weeks in patients with worsening heart failure and preserved ejection fraction (HFpEF)

Summary

EudraCT number	2013-002288-25
Trial protocol	CZ IT AT BE SE DK NL ES HU BG PT GR
Global end of trial date	16 September 2015

Results information

Result version number	v1 (current)
This version publication date	23 September 2016
First version publication date	23 September 2016

Trial information

Trial identification

Sponsor protocol code	BAY1021189/15829

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01951638
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	16 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To find the optimal dose of oral soluble guanylate cyclase (sGC) stimulator BAY1021189 for Phase III that can be given in addition to standard diuretic and comorbidity treatment by characterizing the safety, tolerability, pharmacodynamic effects, and pharmacokinetics, and detecting a significant dose-response relationship in at least one of the two primary end points change in N-terminal pro-brain natriuretic peptide (NT-ProBNP) and change of left atrial volume at 12 weeks in subjects with worsening chronic heart failure and preserved ejection fraction (HFpEF).

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. 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	06 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	Netherlands: 3
Country: Number of subjects enrolled	Poland: 37
Country: Number of subjects enrolled	Portugal: 9
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	Sweden: 9
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Austria: 40
Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	Bulgaria: 69
Country: Number of subjects enrolled	Czech Republic: 16
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Greece: 17

Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	Italy: 28
Country: Number of subjects enrolled	Singapore: 6
Country: Number of subjects enrolled	Taiwan: 19
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Japan: 39
Country: Number of subjects enrolled	Israel: 39
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 2
Country: Number of subjects enrolled	United States: 32
Country: Number of subjects enrolled	Australia: 9
Worldwide total number of subjects	477
EEA total number of subjects	324

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)	80
From 65 to 84 years	350
85 years and over	47

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 158 centers in 25 countries between 06 November 2013 (first subject first visit) and 16 September 2015 (last subject last visit).

Pre-assignment

Screening details:

Overall, 632 subjects were enrolled, of them 477 were randomized and 475 were treated. Among the 477 subjects who were randomized, 404 subjects completed both treatment and follow-up [FU] 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	Subject, Investigator, Carer, Assessor

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	
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 mg

Arm description:

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

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 2.5 mg 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 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 2.5 mg once daily with potential up-titration to 5 mg after 14 or 28 days. Sham titration included on Day 28.

Arm title	BAY1021189 2.5 mg 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 mg	BAY1021189 2.5 mg
Started	93	96	96
Completed	80	82	83
Not completed	13	14	13
Consent withdrawn by subject	9	6	4
Logistical difficulties	-	1	1
Adverse Event	3	4	8
Death	-	-	-
Protocol-driven decision point	1	3	-
Protocol deviation	-	-	-

Number of subjects in period 1	BAY1021189 2.5 mg to 5 mg	BAY1021189 2.5 mg to 10 mg
Started	96	96
Completed	80	86
Not completed	16	10
Consent withdrawn by subject	5	4
Logistical difficulties	-	-
Adverse Event	6	5
Death	3	1
Protocol-driven decision point	-	-
Protocol deviation	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	Subject, Investigator, Carer, Assessor

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

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 2.5 mg 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 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 2.5 mg once daily with potential up-titration to 5 mg after 14 or 28 days. Sham titration included on Day 28.

Arm title	BAY1021189 2.5 mg 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 mg	BAY1021189 2.5 mg
Started	89	95	95
Completed	87	86	90
Not completed	2	9	5
Consent withdrawn by subject	1	5	2
Logistical difficulties	-	2	-
Adverse Event	-	1	2
Death	1	-	1

Lost to follow-up	-	1	-
Protocol deviation	-	-	-

Number of subjects in period 2	BAY1021189 2.5 mg to 5 mg	BAY1021189 2.5 mg to 10 mg
Started	88	94
Completed	80	89
Not completed	8	5
Consent withdrawn by subject	1	2
Logistical difficulties	-	1
Adverse Event	1	1
Death	4	1
Lost to follow-up	1	-
Protocol deviation	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 mg
Reporting group description:	
Subjects received vericiguat (BAY1021189) 1.25 milligram (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 2.5 mg 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 after 14 or 28 days. Sham titration included on Day 28.	
Reporting group title	BAY1021189 2.5 mg 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 mg	BAY1021189 2.5 mg
Number of subjects	93	96	96
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	73.7	73.8	72
standard deviation	± 9.1	± 10	± 10.7
Gender categorical			
Units: Subjects			
Female	46	51	43
Male	47	45	53

Reporting group values	BAY1021189 2.5 mg to 5 mg	BAY1021189 2.5 mg to 10 mg	Total
Number of subjects	96	96	477
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	73.9	72.5	
standard deviation	± 7.9	± 10.2	-

Gender categorical Units: Subjects			
Female	43	44	227
Male	53	52	250

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 mg
Reporting group description:	
Subjects received vericiguat (BAY1021189) 1.25 milligram (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 2.5 mg 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 after 14 or 28 days. Sham titration included on Day 28.	
Reporting group title	BAY1021189 2.5 mg 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 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 2.5 mg 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 after 14 or 28 days. Sham titration included on Day 28.	
Reporting group title	BAY1021189 2.5 mg 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 = 477) included all subjects who were randomized to treatment.	
Subject analysis set title	Safety Analysis Set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
SAF (N = 475) included all subjects from FAS who had at least one dose of study drug administered.	
Subject analysis set title	Per Protocol Set (PPS) NT-pro BNP
Subject analysis set type	Per protocol

Subject analysis set description:

PPS NT-pro BNP (N=345) included all subjects randomized to treatment who had a valid measurement of NT-pro BNP at baseline and at Week 12 (Visit 5) and showed no major protocol deviations.

Subject analysis set title	PPS Left Atrial Volume (LAV)
Subject analysis set type	Per protocol

Subject analysis set description:

PPS LAV (N=338) included all subjects randomized to treatment who had a valid measurement of LAV at baseline and at Week 12 (Visit 5) and showed no major protocol deviations.

Subject analysis set title	Pooled BAY1021189 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 = 195). The three highest dose arms (BAY1021189 2.5mg, 2.5-5mg, and 2.5-10mg) were pooled and used for the primary analysis of the primary end point. 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 the database.

Subject analysis set title	SAF excluding subjects with incorrectly assigned dose
Subject analysis set type	Safety analysis

Subject analysis set description:

SAF excluding subjects with incorrectly assigned dose (N = 427) included all subjects from the SAF except 48 subjects who received lower than planned doses owing to an erroneous software update of the drug dispensation system.

Primary: Change From Baseline to Week 12 in Log-transformed N-terminal Pro-brain Natriuretic Peptide (NT-proBNP)

End point title	Change From Baseline to Week 12 in Log-transformed N-terminal Pro-brain Natriuretic Peptide (NT-proBNP)

End point description:

NTproBNP is a circulating plasma biomarker of cardiovascular function and prognosis in heart failure (HF).

End point type	Primary

End point timeframe:

Baseline, Week 12 (end of treatment [EOT])

End point values	Placebo	BAY1021189 1.25 mg	BAY1021189 2.5 mg	BAY1021189 2.5 mg to 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73[1]	77[2]	78[3]	57[4]
Units: log-transformed picograms per milliliter				
arithmetic mean (standard deviation)	-0.098 (± 0.778)	-0.047 (± 0.788)	0.071 (± 0.818)	0.057 (± 0.819)

Notes:

[1] - PPS NT-proBNP

[2] - PPS NT-proBNP

[3] - PPS NT-proBNP

[4] - PPS NT-proBNP

End point values	BAY1021189 2.5 mg to 10 mg	Pooled BAY1021189 2.5 mg up to 10 mg		

Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	60[5]	195[6]		
Units: log-transformed picograms per milliliter				
arithmetic mean (standard deviation)	-0.023 (± 0.705)	0.038 (± 0.782)		

Notes:

[5] - PPS NT-proBNP

[6] - PPS NT-proBNP

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

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

Comparison groups	Placebo v Pooled BAY1021189 2.5 mg up to 10 mg
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8991
Method	t-test, 1-sided
Parameter estimate	Log-Scale mean difference
Point estimate	0.137
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.04
upper limit	0.31

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

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	BAY1021189 2.5 mg to 10 mg v Placebo
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7194
Method	t-test, 1-sided
Parameter estimate	Log-Scale mean difference
Point estimate	0.076

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.33

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

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	BAY1021189 2.5 mg to 5 mg v Placebo
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8653
Method	t-test, 1-sided
Parameter estimate	Log-Scale mean difference
Point estimate	0.156
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.43

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

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	BAY1021189 2.5 mg v Placebo
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9041
Method	t-test, 1-sided
Parameter estimate	Log-Scale mean difference
Point estimate	0.171
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.43

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

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	BAY1021189 1.25 mg v Placebo
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6572
Method	t-test, 1-sided
Parameter estimate	Log-Scale mean difference
Point estimate	0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.3

Primary: Change From Baseline to Week 12 in Left Atrial Volume (LAV)

End point title	Change From Baseline to Week 12 in Left Atrial Volume (LAV)

End point description:

Left atrial volume was measured by echocardiography.

End point type	Primary

End point timeframe:

Baseline, Week 12 (EOT)

End point values	Placebo	BAY1021189 1.25 mg	BAY1021189 2.5 mg	BAY1021189 2.5 mg to 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	67[7]	77[8]	78[9]	57[10]
Units: milliliter				
arithmetic mean (standard deviation)	-3.361 (± 12.654)	-2.163 (± 7.895)	-2.142 (± 11.931)	-1.252 (± 16.139)

Notes:

[7] - PPS LAV

[8] - PPS LAV

[9] - PPS LAV

[10] - PPS LAV

End point values	BAY1021189 2.5 mg to 10 mg	Pooled BAY1021189 2.5 mg up to 10 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	59[11]	194[12]		
Units: milliliter				

arithmetic mean (standard deviation)	-1.654 (± 10.245)	-1.732 (± 12.808)		

Notes:

[11] - PPS LAV

[12] - PPS LAV

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. The Hochberg procedure was used to test the two primary end points at study-wise significance level of 5%. Results are reported including 90% confidence intervals (CI) for the difference of means.

Comparison groups	Placebo v Pooled BAY1021189 2.5 mg up to 10 mg
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8156
Method	t-test, 1-sided
Parameter estimate	Mean difference (net)
Point estimate	1.629
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.36
upper limit	4.62

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

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 to 10 mg
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7945
Method	t-test, 1-sided
Parameter estimate	Mean difference (net)
Point estimate	1.707
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.39
upper limit	5.8

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

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 to 5 mg
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7917
Method	t-test, 1-sided
Parameter estimate	Mean difference (net)
Point estimate	2.109
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.01
upper limit	7.23

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

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	145
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7241
Method	t-test, 1-sided
Parameter estimate	Mean difference (net)
Point estimate	1.219
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.82
upper limit	5.26

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

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 mg
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7546
Method	t-test, 1-sided
Parameter estimate	Mean difference (net)
Point estimate	1.198
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.23
upper limit	4.63

Other pre-specified: Change From Baseline to Week 12 Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP)

End point title	Change From Baseline to Week 12 Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP)

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 (EOT)

End point values	Placebo	BAY1021189 1.25 mg	BAY1021189 2.5 mg	BAY1021189 2.5 mg to 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	93[13]	96[14]	95[15]	75[16]
Units: millimeter of mercury				
arithmetic mean (standard deviation)				
Change in SBP: (n=80,82,83,61,61)	1.458 (± 18.865)	0.703 (± 16.993)	-1.819 (± 19.438)	-1.486 (± 17.179)
Change in DBP: (n=80,82,83,61,61)	1.887 (± 11.435)	0.911 (± 10.037)	-2.173 (± 11.249)	-1.142 (± 11.4)

Notes:

[13] - SAF

[14] - SAF

[15] - SAF

[16] - SAF excluding subjects with incorrectly assigned dose

End point values	BAY1021189 2.5 mg to 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	68[17]			

Units: millimeter of mercury				
arithmetic mean (standard deviation)				
Change in SBP: (n=80,82,83,61,61) Change in DBP: (n=80,82,83,61,61)	-0.913 (± 15.498) -0.629 (± 10.271)			

Notes:

[17] - SAF excluding subjects with incorrectly assigned dose

Statistical analyses

No statistical analyses for this end point

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

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

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.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 12 (EOT)

End point values	Placebo	BAY1021189 1.25 mg	BAY1021189 2.5 mg	BAY1021189 2.5 mg to 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80[18]	82[19]	83[20]	61[21]
Units: beats per minute				
arithmetic mean (standard deviation)	3.287 (± 13.582)	1.776 (± 11.42)	-0.373 (± 9.845)	1.055 (± 13.331)

Notes:

[18] - SAF with subjects evaluable for this end point.

[19] - SAF with subjects evaluable for this end point.

[20] - SAF with subjects evaluable for this end point.

[21] - SAF excluding subjects with incorrectly assigned dose, with subjects evaluable for this end point.

End point values	BAY1021189 2.5 mg to 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	61[22]			
Units: beats per minute				
arithmetic mean (standard deviation)	-2.623 (± 9.639)			

Notes:

[22] - SAF excluding subjects with incorrectly assigned dose, with subjects evaluable for this end point.

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Subjects With Clinical Events (Heart Failure 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 up to Week 16 including 12 week treatment period and 4 week follow-up period

End point values	Placebo	BAY1021189 1.25 mg	BAY1021189 2.5 mg	BAY1021189 2.5 mg to 5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	93[23]	96[24]	96[25]	96[26]
Units: subjects				
HF hospitalizations	8	6	11	8
CV Mortality	1	0	0	5

Notes:

[23] - FAS

[24] - FAS

[25] - FAS

[26] - FAS

End point values	BAY1021189 2.5 mg to 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	96[27]			
Units: subjects				
HF hospitalizations	5			
CV Mortality	1			

Notes:

[27] - 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 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.

Serious adverse events	Placebo	BAY1021189 1.25 mg	BAY1021189 2.5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 93 (21.51%)	20 / 96 (20.83%)	24 / 95 (25.26%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal stromal tumour			

subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	0 / 95 (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
Hypotension			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	0 / 95 (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
Orthostatic hypotension			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	0 / 95 (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
Surgical and medical procedures			
Eyelid operation			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	0 / 95 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	0 / 95 (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
Pain			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Sudden death			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	0 / 95 (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	1 / 93 (1.08%)	0 / 96 (0.00%)	0 / 95 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 93 (1.08%)	1 / 96 (1.04%)	0 / 95 (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
Epistaxis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	0 / 95 (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 hypertension			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	0 / 95 (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
Respiratory failure			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	0 / 95 (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			
Coagulation time prolonged			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	0 / 95 (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
Intraocular pressure increased			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	0 / 95 (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
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	0 / 95 (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
Ulna fracture			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	0 / 95 (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 pseudoaneurysm			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	0 / 95 (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
Contusion			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	0 / 95 (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
Post procedural haematoma			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	0 / 95 (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

Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 93 (1.08%)	1 / 96 (1.04%)	0 / 95 (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
Atrial fibrillation			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	2 / 95 (2.11%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	6 / 93 (6.45%)	4 / 96 (4.17%)	7 / 95 (7.37%)
occurrences causally related to treatment / all	0 / 6	1 / 4	0 / 12
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	1 / 93 (1.08%)	1 / 96 (1.04%)	3 / 95 (3.16%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	2 / 93 (2.15%)	4 / 96 (4.17%)	3 / 95 (3.16%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	2 / 93 (2.15%)	0 / 96 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	0 / 95 (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
Myocardial infarction			

subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	0 / 95 (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
Tachyarrhythmia			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	0 / 95 (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
Acute coronary syndrome			
subjects affected / exposed	0 / 93 (0.00%)	2 / 96 (2.08%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	0 / 95 (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
Cerebral haemorrhage			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	0 / 95 (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 / 93 (0.00%)	0 / 96 (0.00%)	0 / 95 (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
Cervicogenic headache			

subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	0 / 95 (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	2 / 93 (2.15%)	1 / 96 (1.04%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia of chronic disease			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	0 / 95 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	0 / 95 (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
Eye disorders			
Vitreous haemorrhage			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	0 / 95 (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			
Diarrhoea			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	0 / 95 (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
Large intestine polyp			

subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal haemorrhage			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	0 / 95 (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			
Cholelithiasis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	0 / 95 (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
Jaundice cholestatic			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	0 / 95 (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			
Diabetic foot			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	0 / 95 (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
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	0 / 95 (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 kidney injury			
subjects affected / exposed	2 / 93 (2.15%)	1 / 96 (1.04%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteochondrosis			

subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	0 / 95 (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
Infections and infestations			
Carbuncle			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	0 / 95 (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
Diabetic gangrene			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	0 / 95 (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
Erysipelas			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	0 / 95 (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
Gangrene			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	0 / 95 (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
Gastroenteritis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	0 / 95 (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
Hepatitis C			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	0 / 95 (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
Osteomyelitis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	0 / 95 (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 / 93 (1.08%)	1 / 96 (1.04%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	1 / 95 (1.05%)
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 / 93 (0.00%)	0 / 96 (0.00%)	0 / 95 (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
Urosepsis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	0 / 95 (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
Urinary tract infection bacterial			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	0 / 95 (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
Enterococcal sepsis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	0 / 95 (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
Chlamydial infection			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	0 / 95 (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 tract infection			
subjects affected / exposed	1 / 93 (1.08%)	0 / 96 (0.00%)	0 / 95 (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
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	0 / 93 (0.00%)	0 / 96 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 93 (0.00%)	1 / 96 (1.04%)	0 / 95 (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

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	18 / 95 (18.95%)	21 / 96 (21.88%)	
number of deaths (all causes)	7	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stromal tumour			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypotension			

subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (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			
Eyelid operation			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (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 / 95 (1.05%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			

subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 95 (1.05%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Coagulation time prolonged			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraocular pressure increased			

subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (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			
Femoral neck fracture			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (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	1 / 95 (1.05%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (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	5 / 95 (5.26%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 8	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	2 / 95 (2.11%)	4 / 96 (4.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	3 / 95 (3.16%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			

subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicogenic headache			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of chronic disease			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vitreous haemorrhage			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 95 (1.05%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			

subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (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	4 / 95 (4.21%)	3 / 96 (3.13%)	
occurrences causally related to treatment / all	1 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteochondrosis			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (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			
Carbuncle			

subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gangrene			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (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	0 / 95 (0.00%)	3 / 96 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory syncytial virus bronchiolitis			

subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (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 / 95 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (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 bacterial			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chlamydial infection			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 95 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			

subjects affected / exposed	0 / 95 (0.00%)	0 / 96 (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 / 95 (0.00%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 0	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 mg	BAY1021189 2.5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 93 (22.58%)	33 / 96 (34.38%)	40 / 95 (42.11%)
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 93 (1.08%)	4 / 96 (4.17%)	4 / 95 (4.21%)
occurrences (all)	1	4	6
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	5 / 93 (5.38%)	1 / 96 (1.04%)	3 / 95 (3.16%)
occurrences (all)	5	1	4
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 93 (3.23%)	2 / 96 (2.08%)	10 / 95 (10.53%)
occurrences (all)	3	4	11
Headache			
subjects affected / exposed	1 / 93 (1.08%)	1 / 96 (1.04%)	6 / 95 (6.32%)
occurrences (all)	1	1	6
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 93 (2.15%)	2 / 96 (2.08%)	3 / 95 (3.16%)
occurrences (all)	3	2	3
Oedema peripheral			
subjects affected / exposed	2 / 93 (2.15%)	3 / 96 (3.13%)	2 / 95 (2.11%)
occurrences (all)	3	4	3
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	1 / 93 (1.08%)	1 / 96 (1.04%)	5 / 95 (5.26%)
occurrences (all)	1	1	5
Nausea			
subjects affected / exposed	2 / 93 (2.15%)	2 / 96 (2.08%)	4 / 95 (4.21%)
occurrences (all)	2	2	5
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 93 (1.08%)	5 / 96 (5.21%)	6 / 95 (6.32%)
occurrences (all)	1	5	6
Dyspnoea			
subjects affected / exposed	3 / 93 (3.23%)	6 / 96 (6.25%)	9 / 95 (9.47%)
occurrences (all)	3	7	10
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 93 (2.15%)	5 / 96 (5.21%)	0 / 95 (0.00%)
occurrences (all)	3	5	0
Acute kidney injury			
subjects affected / exposed	1 / 93 (1.08%)	1 / 96 (1.04%)	0 / 95 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 93 (1.08%)	1 / 96 (1.04%)	2 / 95 (2.11%)
occurrences (all)	1	1	2
Nasopharyngitis			
subjects affected / exposed	3 / 93 (3.23%)	4 / 96 (4.17%)	6 / 95 (6.32%)
occurrences (all)	3	4	8
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 93 (0.00%)	6 / 96 (6.25%)	2 / 95 (2.11%)
occurrences (all)	0	6	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	38 / 95 (40.00%)	33 / 96 (34.38%)	
Vascular disorders			

Hypotension			
subjects affected / exposed	5 / 95 (5.26%)	2 / 96 (2.08%)	
occurrences (all)	5	2	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	3 / 95 (3.16%)	2 / 96 (2.08%)	
occurrences (all)	3	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 95 (6.32%)	7 / 96 (7.29%)	
occurrences (all)	6	7	
Headache			
subjects affected / exposed	4 / 95 (4.21%)	4 / 96 (4.17%)	
occurrences (all)	4	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 95 (6.32%)	4 / 96 (4.17%)	
occurrences (all)	6	4	
Oedema peripheral			
subjects affected / exposed	6 / 95 (6.32%)	1 / 96 (1.04%)	
occurrences (all)	7	1	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 95 (2.11%)	0 / 96 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	5 / 95 (5.26%)	4 / 96 (4.17%)	
occurrences (all)	5	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 95 (2.11%)	2 / 96 (2.08%)	
occurrences (all)	2	2	
Dyspnoea			
subjects affected / exposed	5 / 95 (5.26%)	3 / 96 (3.13%)	
occurrences (all)	6	3	
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	1 / 95 (1.05%)	0 / 96 (0.00%)	
occurrences (all)	1	0	
Acute kidney injury			
subjects affected / exposed	5 / 95 (5.26%)	1 / 96 (1.04%)	
occurrences (all)	5	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 95 (4.21%)	6 / 96 (6.25%)	
occurrences (all)	4	6	
Nasopharyngitis			
subjects affected / exposed	1 / 95 (1.05%)	5 / 96 (5.21%)	
occurrences (all)	1	5	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	3 / 95 (3.16%)	3 / 96 (3.13%)	
occurrences (all)	3	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 July 2014	The purpose of amendment was to implement clarifications primarily in exclusion criteria, additions in the study procedures and to correct minor errors or omissions.

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.

End points, "Health-related quality of life, Composite Congestion Score, NYHA function class, echo parameters other than LAV, biomarker and background HF therapies" were exploratory. "Incidence of atrial fibrillation" is reported in AE section.

Notes: