

**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 | 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 | 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 | 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 | 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 (\pm 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 approximately 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 (\pm 12.897) | -0.352 (\pm 10.153) | -1.556 (\pm 10.2) | -0.99 (\pm 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 (\pm 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 occurrences (all) | 3 / 92 (3.26%) 4 | 5 / 91 (5.49%) 6 | 3 / 90 (3.33%) 3 |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) | 5 / 92 (5.43%) 5 | 1 / 91 (1.10%) 1 | 3 / 90 (3.33%) 3 |
| Cough subjects affected / exposed occurrences (all) | 6 / 92 (6.52%) 7 | 8 / 91 (8.79%) 8 | 4 / 90 (4.44%) 4 |
| Metabolism and nutrition disorders Hyperuricaemia subjects affected / exposed occurrences (all) | 1 / 92 (1.09%) 1 | 0 / 91 (0.00%) 0 | 2 / 90 (2.22%) 2 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 3 / 92 (3.26%) 3 | 5 / 91 (5.49%) 5 | 2 / 90 (2.22%) 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 occurrences (all) | 4 / 91 (4.40%) 4 | 14 / 91 (15.38%) 17 | |
| Cardiac disorders Cardiac failure chronic subjects affected / exposed occurrences (all) | 2 / 91 (2.20%) 2 | 0 / 91 (0.00%) 0 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 2 / 91 (2.20%) 2 | 5 / 91 (5.49%) 5 | |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) | 5 / 91 (5.49%) 5 | 2 / 91 (2.20%) 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 | |
| Respiratory, thoracic and mediastinal disorders | Nausea | | | |
| | subjects affected / exposed | 1 / 91 (1.10%) | 1 / 91 (1.10%) | |
| | occurrences (all) | 1 | 1 | |
| | Dyspnoea | | | |
| | subjects affected / exposed | 2 / 91 (2.20%) | 4 / 91 (4.40%) | |
| | occurrences (all) | 3 | 4 | |
| Metabolism and nutrition disorders | Cough | | | |
| | subjects affected / exposed | 4 / 91 (4.40%) | 4 / 91 (4.40%) | |
| | occurrences (all) | 4 | 4 | |
| | 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 | <p>The purpose of this global amendment was to implement clarifications (primarily in exclusion criteria and study procedures):</p> <p>Exclusion criteria were clarified to facilitate enrollment of appropriate subjects, to prevent over-interpretation and exclusion of eligible subjects, and to minimize protocol deviations:</p> <ul style="list-style-type: none">-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 $>40 \text{ kg/m}^2$ to $>45 \text{ kg/m}^2$ 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. <p>Study procedures were clarified to minimize protocol deviations.</p> <p>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.</p> <p>IV vasodilators were included as indicative of worsening chronic heart failure (WCHF) to be consistent with the CEC manual.</p> <p>The protocol was clarified in that HR was also measured during echocardiography.</p> |

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: