



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled, Cross-over Phase 2 Study of Continuous 8-Hour Intravenous Infusions of BMS-986231 in Patients with Heart Failure and Impaired Systolic Function Given a Standard Dose of Loop Diuretic

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | CV013-034 |
|-----------------------|-----------|

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 14 February 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 09 January 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

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

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Period 1

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

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Sequence 1 |

Arm description:

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

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

Dosage and administration details:

Dosed period 2

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

Dosage and administration details:

Dosed period 1

| | |
|------------------|------------|
| Arm title | Sequence 2 |
|------------------|------------|

Arm description:

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

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

Dosage and administration details:

Dosed period 2

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

Dosage and administration details:

Dosed period 1

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

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 1 participant did not complete Period 2 but remained in the study, completing the study

Baseline characteristics

Reporting groups

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

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

End points

End points reporting groups

| | |
|--|--------------------|
| Reporting group title | Sequence 1 |
| Reporting group description: First received placebo (period 1), then received BMS-986231 (period 2) following washout. Each treatment administered 8 hours continuous IV infusion at the dose of 12 µg/kg/min, corresponding to an infusion rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide administered through a separate IV line, given slowly over 1 to 2 minutes. | |
| Reporting group title | Sequence 2 |
| Reporting group description: First received BMS-986231 (period 1), then received placebo (period 2) following washout. Each treatment administered 8 hours continuous IV infusion at the dose of 12 µg/kg/min, corresponding to an infusion rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide administered through a separate IV line, given slowly over 1 to 2 minutes. | |
| Subject analysis set title | BMS-986231 |
| Subject analysis set type | Per protocol |
| Subject analysis set description: BMS-986231 administered 8 hours continuous IV infusion at the dose of 12 µg/kg/min, corresponding to an infusion rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide administered through a separate IV line, given slowly over 1 to 2 minutes. | |
| Subject analysis set title | Placebo |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Placebo administered 8 hours continuous IV infusion of D5W administered at the flow rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide administered through a separate IV line, given slowly over 1 to 2 minutes. | |
| Subject analysis set title | BMS-986231 |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: BMS-986231 administered 8 hours continuous IV infusion at the dose of 12 µg/kg/min, corresponding to an infusion rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide administered through a separate IV line, given slowly over 1 to 2 minutes. | |
| Subject analysis set title | Placebo |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Placebo administered 8 hours continuous IV infusion of D5W administered at the flow rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide administered through a separate IV line, given slowly over 1 to 2 minutes. | |
| Subject analysis set title | Placebo |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Placebo administered 8 hours continuous IV infusion of D5W administered at the flow rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide administered through a separate IV line, given slowly over 1 to 2 minutes. | |
| Subject analysis set title | BMS-986231 |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: BMS-986231 administered 8 hours continuous IV infusion at the dose of 12 µg/kg/min, corresponding to an infusion rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide administered through a separate IV line, given slowly over 1 to 2 minutes. | |
| Subject analysis set title | BMS-986231 |
| Subject analysis set type | Per protocol |
| Subject analysis set description: BMS-986231 administered 8 hours continuous IV infusion at the dose of 12 µg/kg/min, corresponding to an infusion rate of 20 mL/H. At hour 4 after the start of the infusion, 40 mg IV bolus of furosemide | |

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

| | |
|----------------------------|--------------|
| Subject analysis set title | Placebo |
| Subject analysis set type | Per protocol |

Subject analysis set description:

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

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

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

End point description:

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

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | 4 hours |

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

Statistical analyses

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

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

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

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

| | |
|--|---|
| End point title | FeNa in participants with HFrEF while on BMS-986231 compared to placebo |
| End point description: | |
| Secondary efficacy analyses was performed using the randomized population. The FeNa, FeK, furosemide urinary and plasma concentration and the ratio of urinary sodium to urinary furosemide was calculated at each time point over 4-hour urine/plasma collection after a bolus injection of 40 mg furosemide while receiving BMS-986231 or placebo. Fractional Excretion Na = ((Urine Sodium * Plasma Creatinine) / (Plasma Sodium * Urine Creatinine)) * 100 | |
| End point type | Secondary |
| End point timeframe: | |
| Day 1, predose; 0-4 hours, 4-5 hours, 5-6 hours, 6-7 hours, 7-8 hours | |

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

| | | | | |
|-----------|-------------------|-------------------|--|--|
| 7-8 hours | 1.7 (\pm 1.26) | 3.3 (\pm 2.52) | | |
|-----------|-------------------|-------------------|--|--|

Statistical analyses

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

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

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

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

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

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

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

End point description:

Secondary efficacy analyses was performed using the randomized population. The FeNa, FeK, furosemide urinary and plasma concentration and the ratio of urinary sodium to urinary furosemide was calculated at each time point over 4-hour urine/plasma collection after a bolus injection of 40 mg furosemide while receiving BMS-986231 or placebo. Fractional Excretion K = ((Urine Potassium * Plasma Creatinine) / (Plasma Potassium * Urine Creatinine)) * 100

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

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

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

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

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

Secondary: Furosemide urinary concentrations

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Furosemide plasma concentrations

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

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

Statistical analyses

No statistical analyses for this end point

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

infusion

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

0-4 hours after furosemide

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with clinically relevant hypotension

| | |
|-----------------|---|
| End point title | Number of participants with clinically relevant hypotension |
|-----------------|---|

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

up to 8 hours

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|--|---|
| End point title | Number of participants with an Adverse Event (AE) |
| End point description: Clinically relevant hypotension is defined as systolic blood pressure (SBP) < 90 mmHg or symptomatic hypotension during infusion | |
| End point type | Secondary |
| End point timeframe: up to 8 days | |

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with an Abnormal Clinical Laboratory Value

| | |
|--|---|
| End point title | Number of participants with an Abnormal Clinical Laboratory Value |
| End point description: Number of participants who experienced an in-study abnormal clinical laboratory event under the category of Hematology, Chemistry or Urinalysis. | |
| End point type | Secondary |
| End point timeframe: from first dose to 30 days post-last dose (ca. 5-8 weeks) | |

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

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Vital Signs - blood pressure

| | |
|---|--|
| End point title | Change from baseline in Vital Signs - blood pressure |
| End point description: The change in baseline for vital signs was reported for each arm. | |

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 1, 8 hours post-dose (end of infusion) | |

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

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Vital Signs - heart rate

| | |
|---|--|
| End point title | Change from baseline in Vital Signs - heart rate |
| End point description: | |
| The change in baseline for vital signs was reported for each arm. | |
| End point type | Secondary |
| End point timeframe: | |
| Day 1, 8 hours post-dose (end of infusion) | |

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

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Vital Signs - oxygen saturation

| | |
|---|---|
| End point title | Change from baseline in Vital Signs - oxygen saturation |
| End point description: | |
| The change in baseline for vital signs was reported for each arm. | |
| End point type | Secondary |

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Telemetry

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

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

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Physical Examination - body weight

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

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

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

| | |
|-----------------------|------------|
| Reporting group title | BMS-986231 |
|-----------------------|------------|

Reporting group description:

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported