



Clinical trial results:

An open-label, international, multicenter, single-arm, uncontrolled, phase IIIb study of riociguat in patients with PAH who demonstrate an insufficient response to treatment with phosphodiesterase-5 inhibitors (PDE-5i)

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2013-001759-10 |
| Trial protocol | DE CZ IT BE GB FR |
| Global end of trial date | 29 December 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 |
| This version publication date | 15 December 2017 |
| First version publication date | 15 December 2017 |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | BAY63-2521/16719 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02007629 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Bayer AG |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, Leverkusen D-51368, 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 December 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 December 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To investigate whether it was safe, feasible and beneficial to replace phosphodiesterase-5 inhibitors (PDE-5i) therapy with Riociguat (BAY63-2521) in pulmonary arterial hypertension (PAH) subjects demonstrating insufficient response to PDE-5 inhibition.

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 Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 18 February 2014 |
| 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 States: 3 |
| Country: Number of subjects enrolled | Canada: 1 |
| Country: Number of subjects enrolled | Switzerland: 1 |
| Country: Number of subjects enrolled | United Kingdom: 8 |
| Country: Number of subjects enrolled | Belgium: 2 |
| Country: Number of subjects enrolled | Czech Republic: 8 |
| Country: Number of subjects enrolled | France: 4 |
| Country: Number of subjects enrolled | Germany: 23 |
| Country: Number of subjects enrolled | Italy: 11 |
| Worldwide total number of subjects | 61 |
| EEA total number of subjects | 56 |

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) | 46 |
| From 65 to 84 years | 15 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Study was conducted in 20 study centers in Belgium, Czech Republic, France, Germany, Italy, Switzerland, United Kingdom, Canada, United States, Germany, between 18 February 2014 (first subject first visit) and 29 December 2016 (last subject last visit).

Pre-assignment

Screening details:

Overall, 79 subject were screened, of them 17 were screen failure and 1 withdrew consent; total 61 were assigned to pre-treatment phase (approximately 2 weeks) and treatment phase (titration phase [8 weeks] and maintenance phase [16 weeks]). Of 61 subjects, 51 completed treatment phase and 28 of them entered in an extended drug supply phase (EDSP).

Period 1

| | |
|------------------------------|----------------|
| Period 1 title | Main Phase |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|-----------|---|
| Arm title | Riociguat up to 2.5 mg tid (Main Phase) |
|-----------|---|

Arm description:

Subjects received riociguat film coated immediate-release (IR) tablet 3 times a day (tid) with or without food at a starting dose of 1.0 milligram (mg) and increased by 0.5 mg increments at 2-weekly intervals to a maximum of 2.5 mg tid, until Week 8 (titration phase). An optimal dose was determined based on systolic blood pressure (SBP) and well-being. Thereafter, riociguat continued at the optimal individual dose until Week 24 (Main phase). Dose reductions or stop of study medication for safety reasons were allowed at any time. Increases or re-increases in 0.5 mg steps (maximum dose 2.5 mg) were possible at the investigator's discretion weighing the benefit with potential risks implied.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Riociguat |
| Investigational medicinal product code | BAY63-2521 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received riociguat film coated IR tablet 3 tid with or without food at a starting dose of 1.0 mg and increased by 0.5 mg increments at 2-weekly intervals to a maximum of 2.5 mg tid, until Week 8 (titration phase).

| Number of subjects in period 1 | Riociguat up to 2.5 mg tid (Main Phase) |
|--------------------------------|---|
| Started | 61 |
| Completed | 51 |
| Not completed | 10 |
| Physician decision | 1 |
| Consent withdrawn by subject | 3 |
| Death | 1 |
| Adverse event | 4 |

| | |
|------------------|---|
| Lack of efficacy | 1 |
|------------------|---|

Period 2

| | |
|------------------------------|-----------------------------------|
| Period 2 title | Extended Drug Supply Phase (EDSP) |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------|---------------------------------|
| Arm title | Riociguat up to 2.5 mg tid EDSP |
|------------------|---------------------------------|

Arm description:

Subjects were offered participation in EDSP and received riociguat 2.5 mg film coated IR tablet 3 tid with or without food for 18 months or until reimbursement.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Riociguat |
| Investigational medicinal product code | BAY63-2521 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were offered participation in EDSP and received riociguat 2.5 mg film coated IR tablet 3 tid with or without food for 18 months or until reimbursement.

| | |
|---|---------------------------------|
| Number of subjects in period 2^[1] | Riociguat up to 2.5 mg tid EDSP |
| Started | 28 |
| Completed | 28 |

Notes:

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

Justification: Not all subjects who completed the main phase were enrolled in EDSP. Subjects may continue to participate in EDSP of the study at the discretion of the investigator. The study drug was provided free of charge until market approval and reimbursement or at the longest for 18 months, whatever date occurs earlier.

Baseline characteristics

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Riociguat up to 2.5 mg tid (Main Phase) |
|-----------------------|---|

Reporting group description:

Subjects received riociguat film coated immediate-release (IR) tablet 3 times a day (tid) with or without food at a starting dose of 1.0 milligram (mg) and increased by 0.5 mg increments at 2-weekly intervals to a maximum of 2.5 mg tid, until Week 8 (titration phase). An optimal dose was determined based on systolic blood pressure (SBP) and well-being. Thereafter, riociguat continued at the optimal individual dose until Week 24 (Main phase). Dose reductions or stop of study medication for safety reasons were allowed at any time. Increases or re-increases in 0.5 mg steps (maximum dose 2.5 mg) were possible at the investigator's discretion weighing the benefit with potential risks implied.

| Reporting group values | Riociguat up to 2.5 mg tid (Main Phase) | Total | |
|------------------------|---|-------|--|
| Number of subjects | 61 | 61 | |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--|--------|----|--|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 53.9 | | |
| standard deviation | ± 13.8 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 45 | 45 | |
| Male | 16 | 16 | |
| World Health Organization Functional Class (WHO FC) | | | |
| WHO FC assessment of PAH ranged from functional class I (subjects with pulmonary hypertension [PH] but without resulting limitation of physical activity); class II (subjects with PH resulting in slight limitation of physical activity); class III (subjects with PH resulting in marked limitation of physical activity); class IV (subjects with PH with inability to carry out any physical activity without symptoms); and class V death. Changes to a lower WHO FC resemble improvement; changes to a higher functional class resemble deterioration of PAH. | | | |
| Units: Subjects | | | |
| Class I | 0 | 0 | |
| Class II | 0 | 0 | |
| Class III | 61 | 61 | |
| Class IV | 0 | 0 | |
| Class V | 0 | 0 | |
| Number of subjects with and without idiopathic PAH | | | |
| Number of subjects with and without idiopathic PAH at baseline were reported. | | | |
| Units: Subjects | | | |
| With idiopathic PAH | 56 | 56 | |
| Without idiopathic PAH | 5 | 5 | |
| Number of subjects receiving sildenafil and tadalafil | | | |
| Number of subjects receiving sildenafil and tadalafil before entering RESPITE were reported. | | | |
| Units: Subjects | | | |
| Subjects receiving sildenafil | 40 | 40 | |
| Subjects receiving tadalafil | 21 | 21 | |

| | | | |
|--|-----------|----|--|
| Number of subjects with and without endothelin receptor antagonists (ERAs) therapy | | | |
| Number of subjects with and without ERAs therapy at baseline evaluation were reported. | | | |
| Units: Subjects | | | |
| With ERAs therapy | 50 | 50 | |
| Without ERAs therapy | 11 | 11 | |
| Six-Minute Walking Distance (6MWD) Test | | | |
| 6MWD test was used to measure the subjects functional exercise capacity. Subjects were instructed to walk alone, not run, from one end to the other end of the walking course, at their own pace, while attempting to cover as much ground as possible in 6 minutes. No "warm-up" period was performed before the test. Investigators have not walked with the subjects. This was an encouraged test (the person conducting the test encouraged subjects to walk farther or faster by using only standardized phrases). 61 subjects performed the 6MWD test at baseline. | | | |
| Units: meter | | | |
| arithmetic mean | 356.93 | | |
| standard deviation | ± 80.58 | - | |
| Cardiac Index | | | |
| The cardiac output was measured by using the thermodilution methodology and a respective electronic device. 50 subjects performed the cardiac index test at baseline. The cardiac index was assessed by dividing the cardiac output by the person's body surface area (BSA). | | | |
| Units: liters per minute per square meter | | | |
| arithmetic mean | 2.32 | | |
| standard deviation | ± 0.42 | - | |
| Pulmonary vascular resistance (PVR) | | | |
| Baseline value of PVR was calculated in 51 subjects. | | | |
| Units: dyne*second*centimeter ⁻⁵ | | | |
| arithmetic mean | 835.36 | | |
| standard deviation | ± 272.33 | - | |
| N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) | | | |
| Baseline value of NT-proBNP was calculated in 61 subjects. | | | |
| Units: picogram per milliliter (pg/mL) | | | |
| arithmetic mean | 1189.62 | | |
| standard deviation | ± 1827.76 | - | |
| EuroQol questionnaire (EQ-5D) | | | |
| EQ-5D was a standardized instrument which was used to measure the health outcome. The EQ-5D was a selfreport questionnaire and need to be completed by the subject. After the subject has filled in the questionnaire, the questionnaire was transferred into the electronic case report form (eCRF). EQ-5D was calculated by two types of questionnaires Part A (descriptive health profile) and Part B (visual analogue scale). | | | |
| Units: score on a scale | | | |
| arithmetic mean | 62 | | |
| standard deviation | ± 17.7 | - | |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Riociguat up to 2.5 mg tid (Main Phase) |
| Reporting group description: Subjects received riociguat film coated immediate-release (IR) tablet 3 times a day (tid) with or without food at a starting dose of 1.0 milligram (mg) and increased by 0.5 mg increments at 2-weekly intervals to a maximum of 2.5 mg tid, until Week 8 (titration phase). An optimal dose was determined based on systolic blood pressure (SBP) and well-being. Thereafter, riociguat continued at the optimal individual dose until Week 24 (Main phase). Dose reductions or stop of study medication for safety reasons were allowed at any time. Increases or re-increases in 0.5 mg steps (maximum dose 2.5 mg) were possible at the investigator's discretion weighing the benefit with potential risks implied. | |
| Reporting group title | Riociguat up to 2.5 mg tid EDSP |
| Reporting group description: Subjects were offered participation in EDSP and received riociguat 2.5 mg film coated IR tablet 3 tid with or without food for 18 months or until reimbursement. | |
| Subject analysis set title | Full Analysis Set (FAS) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: FAS (N=61) included all subjects who were included in the study, were assigned to study treatment, and received at least one dose of study drug. | |

Primary: Change From Pre-treatment in 6 Minute Walking Distance (6MWD)

| | |
|--|--|
| End point title | Change From Pre-treatment in 6 Minute Walking Distance (6MWD) ^[1] |
| End point description: 6MWD test was used to measure the subjects functional exercise capacity. Subjects were instructed to walk alone, not run, from one end to the other end of the walking course, at their own pace, while attempting to cover as much ground as possible in 6 minutes. No "warm-up" period was performed before the test. Investigators have not walked with the subjects. This was an encouraged test (the person conducting the test encouraged subjects to walk farther or faster by using only standardized phrases). In the below table 'n' signifies number of evaluable subjects for the respective category. | |
| End point type | Primary |
| End point timeframe: Baseline, Week 12 and Week 24 | |
| Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No formal statistical testing was planned. | |

| End point values | Riociguat up to 2.5 mg tid (Main Phase) | | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 52 ^[2] | | | |
| Units: meter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Week 12 (n=52) | 24.42 (± 57.28) | | | |
| Change at Week 24 (n=51) | 31 (± 63.32) | | | |

Notes:

[2] - FAS with evaluable subjects for this end point.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Cardiac Index

| | |
|-----------------|---------------------------------------|
| End point title | Change From Baseline in Cardiac Index |
|-----------------|---------------------------------------|

End point description:

The cardiac output was measured by using the thermodilution methodology and a respective electronic device. The cardiac index was assessed by dividing the cardiac output by the person's BSA.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline, Week 24

| | | | | |
|--|---|--|--|--|
| End point values | Riociguat up to 2.5 mg tid (Main Phase) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 48 ^[3] | | | |
| Units: liter per minute per square meter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Week 24 | 0.32 (± 0.53) | | | |

Notes:

[3] - FAS with evaluable subjects for this end point.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Pre-treatment in N-Terminal Pro-Brain Natriuretic Peptide (NTproBNP)

| | |
|-----------------|--|
| End point title | Change From Pre-treatment in N-Terminal Pro-Brain Natriuretic Peptide (NTproBNP) |
|-----------------|--|

End point description:

NT-proBNP cardiac biomarker was used to detect, diagnose, and evaluate the severity of heart failure. A higher level of the marker was indicative of heart failure. In the below table 'n' signifies number of evaluable subjects for the respective category.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline, Week 12 and Week 24

| | | | | |
|--|---|--|--|--|
| End point values | Riociguat up to 2.5 mg tid (Main Phase) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 54 ^[4] | | | |
| Units: picogram per milliliter (pg/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Week 12 (n=54) | -77.17 (± 1251.99) | | | |

| | | | | |
|--------------------------|---------------------|--|--|--|
| Change at Week 24 (n=52) | -347.12 (± 1235.21) | | | |
|--------------------------|---------------------|--|--|--|

Notes:

[4] - FAS with evaluable subjects for this end point.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in World Health Organization Functional Class (WHO FC)

| | |
|-----------------|---|
| End point title | Change From Baseline in World Health Organization Functional Class (WHO FC) |
|-----------------|---|

End point description:

WHO FC assessment of PAH ranged from functional class I (subjects with PH but without resulting limitation of physical activity); class II (subjects with PH resulting in slight limitation of physical activity); class III (subjects with PH resulting in marked limitation of physical activity); class IV (subjects with PH with inability to carry out any physical activity without symptoms); and class V death. Changes to a lower WHO FC resemble improvement; changes to a higher functional class resemble deterioration of PAH. In the below table 'n' signifies number of evaluable subjects for the respective category.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline, Week 12 and Week 24

| End point values | Riociguat up to 2.5 mg tid (Main Phase) | | | |
|-------------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 54 ^[5] | | | |
| Units: subjects | | | | |
| Change at Week 12 (n=54): WHO FC -2 | 1 | | | |
| Change at Week 12 (n=54): WHO FC -1 | 26 | | | |
| Change at Week 12 (n=54): WHO FC 0 | 27 | | | |
| Change at Week 12 (n=54): WHO FC 1 | 0 | | | |
| Change at Week 12 (n=54): WHO FC 2 | 0 | | | |
| Change at Week 24 (n=52): WHO FC -2 | 1 | | | |
| Change at Week 24 (n=52): WHO FC -1 | 27 | | | |
| Change at Week 24 (n=52): WHO FC 0 | 24 | | | |
| Change at Week 24 (n=52): WHO FC 1 | 0 | | | |
| Change at Week 24 (n=52): WHO FC 2 | 0 | | | |

Notes:

[5] - FAS with evaluable subjects for this end point.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects With Clinical Worsening

| | |
|--|--|
| End point title | Percentage of Subjects With Clinical Worsening |
| End point description: | |
| Clinical worsening was defined as death (all-cause mortality); atrial septostomy; lung transplantation; non-planned PAH-related hospitalisation; start of new PAH treatment (ERA, inhaled or oral prostanoid) or modification of pre-existing treatment, initiation of intravenous or subcutaneous prostanoids; persistent decrease of greater than (>) 15% from baseline or >30% from last measurement in 6MWD; persistent worsening of WHO FC; or appearance or worsening of signs/symptoms of right heart failure not responding to optimised oral diuretic therapy. All identified and suspected clinical worsening events were confirmed by independent central adjudication. | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Baseline to Week 24 | |

| | | | | |
|-------------------------------|---|--|--|--|
| End point values | Riociguat up to 2.5 mg tid (Main Phase) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 61 ^[6] | | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 9.8 | | | |

Notes:

[6] - FAS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in European Quality of life (QoL)-Group (EQ)-5D Questionnaire

| | |
|---|--|
| End point title | Change From Baseline in European Quality of life (QoL)-Group (EQ)-5D Questionnaire |
| End point description: | |
| EQ-5D was a standardized instrument which was used to measure the health outcome. The EQ-5D was a selfreport questionnaire and needed to be completed by the subject. After the subject filled in the questionnaire, the questionnaire was transferred into the electronic case report form (eCRF). EQ-5D was calculated by two types of questionnaires Part A (descriptive health profile) and Part B (visual analogue scale). Part A, EQ-5D comprised 5-item questionnaires to measure own health profile status (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each measure has three levels (1. no problems, 2. some problems, 3. extreme problems). In Part B, visual analogue rating scale to measure how good or bad a health state was. Scale was drawn by using thermometer-like scale, on which the best state imagine was marked as 100 and worst state imagine was marked as 0. In the below table 'n' signifies number of evaluable subjects for the respective category. | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Baseline, Week 12 and Week 24 | |

| | | | | |
|--|---|--|--|--|
| End point values | Riociguat up to 2.5 mg tid (Main Phase) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 52 ^[7] | | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| EQ-5D-Visual Analog Scale:Change at Week 12 (n=52) | 6.1 (± 15.4) | | | |
| EQ-5D-Visual Analog Scale:Change at Week 24 (n=52) | 6.5 (± 19.4) | | | |
| EQ-5D-Utility score: Change at Week 12 (n=51) | 0.07 (± 0.29) | | | |
| EQ-5D-Utility score: Change at Week 24 (n=52) | 0.07 (± 0.28) | | | |

Notes:

[7] - FAS with evaluable subjects for this end point.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects Without Clinical Worsening who Achieve at Least WHO FC II and an Improvement in 6 MWD of Greater Than or Equal to (≥) 30 meters

| | |
|-----------------|--|
| End point title | Percentage of Subjects Without Clinical Worsening who Achieve at Least WHO FC II and an Improvement in 6 MWD of Greater Than or Equal to (≥) 30 meters |
|-----------------|--|

End point description:

Percentage of subjects without clinical worsening who achieve at least who FC II and an improvement in 6 MWD of ≥ 30 meters were reported. In the below table 'n' signifies number of evaluable subjects for the respective category.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline, Week 12 and Week 24

| | | | | |
|----------------------------------|---|--|--|--|
| End point values | Riociguat up to 2.5 mg tid (Main Phase) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 54 ^[8] | | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| WHO FC II, Week 12: No (n=27) | 50 | | | |
| WHO FC II, Week 12: Yes (n=27) | 50 | | | |
| WHO FC II, Week 24: No (n=24) | 46.2 | | | |
| WHO FC II, Week 24: Yes (n=28) | 53.8 | | | |
| 6 MWD ≥30 m, Week 12: No (n=24) | 46.2 | | | |
| 6 MWD ≥30 m, Week 12: Yes (n=28) | 53.8 | | | |
| 6 MWD ≥30 m, Week 24: No (n=25) | 49 | | | |
| 6 MWD ≥30 m, Week 24: Yes (n=26) | 51 | | | |

Notes:

[8] - FAS with evaluable subjects for this end point.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study treatment up to 30 days after last study drug intake for main phase and from start of study treatment in EDSP up to the end of study in EDSP subjects

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Riociguat up to 2.5 mg tid Main phase |
|-----------------------|---------------------------------------|

Reporting group description:

Subjects received riociguat (BAY63-2521) film coated IR tablet tid with or without food at a starting dose of 1.0 mg and increased by 0.5 mg increments at 2-weekly intervals to a maximum of 2.5 mg tid, until Week 8 (titration phase). An optimal dose was determined based on SBP and well-being. Thereafter, riociguat continued at the optimal individual dose until Week 24 (Main phase). Dose reductions or stop of study medication for safety reasons were allowed at any time. Increases or re-increases in 0.5 mg steps (maximum dose 2.5 mg) were possible at the investigator's discretion weighing the benefit with potential risks implied.

| | |
|-----------------------|---------------------------------|
| Reporting group title | Riociguat up to 2.5 mg tid EDSP |
|-----------------------|---------------------------------|

Reporting group description:

Subjects were offered participation in EDSP and received riociguat 2.5 mg film coated IR tablet 3 tid with or without food for 18 months or until reimbursement. Treatment-emergent adverse events (TEAEs) during EDSP included either ongoing from main phase at the time of entry into EDSP or newly reported in EDSP.

| Serious adverse events | Riociguat up to 2.5 mg tid Main phase | Riociguat up to 2.5 mg tid EDSP | |
|---|---------------------------------------|---------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 10 / 61 (16.39%) | 7 / 28 (25.00%) | |
| number of deaths (all causes) | 5 | 4 | |
| number of deaths resulting from adverse events | 2 | 3 | |
| Injury, poisoning and procedural complications | | | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Vascular disorders | | | |
| Hypotension | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Right ventricular failure | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 0 / 28 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Medical device change | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interventional procedure | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Gastrointestinal disorders | | | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (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 | | | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Depression | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (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 | | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (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 | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Riociguat up to 2.5 mg tid Main phase | Riociguat up to 2.5 mg tid EDSP | |
|---|---------------------------------------|---------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 57 / 61 (93.44%) | 23 / 28 (82.14%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin papilloma | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Colon adenoma | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|--|-----------------------|---------------------|--|
| Monoclonal gammopathy subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 28 (0.00%) 0 | |
| Vascular disorders | | | |
| Flushing subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 1 / 28 (3.57%) 1 | |
| Hypertension subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 28 (3.57%) 1 | |
| Hypotension subjects affected / exposed occurrences (all) | 9 / 61 (14.75%) 10 | 2 / 28 (7.14%) 2 | |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 2 / 61 (3.28%) 2 | 2 / 28 (7.14%) 2 | |
| Chest discomfort subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 28 (0.00%) 0 | |
| Chest pain subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 2 / 28 (7.14%) 2 | |
| Cyst subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 1 / 28 (3.57%) 1 | |
| Fatigue subjects affected / exposed occurrences (all) | 6 / 61 (9.84%) 8 | 0 / 28 (0.00%) 0 | |
| Feeling cold subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 28 (0.00%) 0 | |
| Influenza like illness subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 28 (0.00%) 0 | |
| Injection site inflammation | | | |

| | | | |
|--|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 28 (3.57%) 1 | |
| Oedema subjects affected / exposed occurrences (all) | 3 / 61 (4.92%) 3 | 0 / 28 (0.00%) 0 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 8 / 61 (13.11%) 9 | 1 / 28 (3.57%) 1 | |
| Pyrexia subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 1 / 28 (3.57%) 1 | |
| Puncture site haemorrhage subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 28 (0.00%) 0 | |
| Sensation of foreign body subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 28 (0.00%) 0 | |
| Reproductive system and breast disorders Haematospermia subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 28 (3.57%) 1 | |
| Menorrhagia subjects affected / exposed occurrences (all) | 2 / 61 (3.28%) 2 | 0 / 28 (0.00%) 0 | |
| Haemorrhagic ovarian cyst subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 28 (0.00%) 0 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 5 / 61 (8.20%) 6 | 2 / 28 (7.14%) 2 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 6 / 61 (9.84%) 6 | 4 / 28 (14.29%) 4 | |
| Dyspnoea exertional | | | |

| | | |
|------------------------------------|----------------|----------------|
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 1 |
| Epistaxis | | |
| subjects affected / exposed | 5 / 61 (8.20%) | 2 / 28 (7.14%) |
| occurrences (all) | 6 | 4 |
| Haemoptysis | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 28 (3.57%) |
| occurrences (all) | 1 | 3 |
| Hyperventilation | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 |
| Hypoxia | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 1 |
| Nasal congestion | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 28 (3.57%) |
| occurrences (all) | 2 | 1 |
| Productive cough | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 2 / 28 (7.14%) |
| occurrences (all) | 0 | 2 |
| Pulmonary artery aneurysm | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 |
| Pulmonary hypertension | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 |
| Upper respiratory tract congestion | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 28 (3.57%) |
| occurrences (all) | 1 | 1 |
| Pulmonary arterial hypertension | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 28 (3.57%) |
| occurrences (all) | 1 | 1 |
| Oropharyngeal discomfort | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 |
| Oropharyngeal pain | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 28 (0.00%) 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences (all) | 0 | 1 | |
| Depression | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood potassium decreased | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 2 / 28 (7.14%) | |
| occurrences (all) | 2 | 2 | |
| Blood thyroid stimulating hormone increased | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences (all) | 0 | 1 | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| International normalised ratio increased | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 28 (3.57%) | |
| occurrences (all) | 2 | 1 | |
| Low density lipoprotein increased | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 28 (3.57%) | |
| occurrences (all) | 1 | 1 | |
| Respiratory rate increased | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Weight increased | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Occult blood positive | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 28 (0.00%) 0 | |
| Injury, poisoning and procedural complications | | | |
| Accident | | | |
| subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 28 (3.57%) 1 | |
| Arthropod bite | | | |
| subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 28 (0.00%) 0 | |
| Fall | | | |
| subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 1 / 28 (3.57%) 1 | |
| Overdose | | | |
| subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 28 (0.00%) 0 | |
| Subcutaneous haematoma | | | |
| subjects affected / exposed occurrences (all) | 2 / 61 (3.28%) 2 | 0 / 28 (0.00%) 0 | |
| Contusion | | | |
| subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 1 / 28 (3.57%) 1 | |
| Thermal burn | | | |
| subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 28 (0.00%) 0 | |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed occurrences (all) | 2 / 61 (3.28%) 2 | 1 / 28 (3.57%) 1 | |
| Pericardial effusion | | | |
| subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 1 / 28 (3.57%) 1 | |
| Right ventricular failure | | | |
| subjects affected / exposed occurrences (all) | 4 / 61 (6.56%) 4 | 1 / 28 (3.57%) 1 | |
| Nervous system disorders | | | |

| | | | |
|--------------------------------------|------------------|-----------------|--|
| Cervicobrachial syndrome | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dizziness | | | |
| subjects affected / exposed | 10 / 61 (16.39%) | 0 / 28 (0.00%) | |
| occurrences (all) | 11 | 0 | |
| Dizziness postural | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 28 (3.57%) | |
| occurrences (all) | 2 | 1 | |
| Headache | | | |
| subjects affected / exposed | 12 / 61 (19.67%) | 3 / 28 (10.71%) | |
| occurrences (all) | 18 | 3 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Multiple sclerosis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 28 (3.57%) | |
| occurrences (all) | 1 | 1 | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 2 / 28 (7.14%) | |
| occurrences (all) | 0 | 3 | |
| Sciatica | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences (all) | 0 | 2 | |
| Balance disorder | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences (all) | 0 | 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 1 / 28 (3.57%) | |
| occurrences (all) | 3 | 2 | |
| Increased tendency to bruise | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 28 (0.00%) 0 | |
| Iron deficiency anaemia subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 28 (3.57%) 1 | |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 28 (0.00%) 0 | |
| Vertigo subjects affected / exposed occurrences (all) | 2 / 61 (3.28%) 3 | 0 / 28 (0.00%) 0 | |
| Eye disorders Cataract subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 28 (3.57%) 1 | |
| Eyelid oedema subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 28 (0.00%) 0 | |
| Visual impairment subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 28 (0.00%) 0 | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 2 / 28 (7.14%) 2 | |
| Abdominal pain lower subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 2 | 0 / 28 (0.00%) 0 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 5 / 61 (8.20%) 7 | 2 / 28 (7.14%) 2 | |
| Constipation subjects affected / exposed occurrences (all) | 2 / 61 (3.28%) 2 | 1 / 28 (3.57%) 1 | |
| Diarrhoea | | | |

| | | | |
|----------------------------------|------------------|-----------------|--|
| subjects affected / exposed | 11 / 61 (18.03%) | 4 / 28 (14.29%) | |
| occurrences (all) | 14 | 5 | |
| Dyspepsia | | | |
| subjects affected / exposed | 13 / 61 (21.31%) | 4 / 28 (14.29%) | |
| occurrences (all) | 13 | 4 | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Faeces discoloured | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Flatulence | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 28 (3.57%) | |
| occurrences (all) | 1 | 1 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 28 (3.57%) | |
| occurrences (all) | 2 | 1 | |
| Haematochezia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 28 (3.57%) | |
| occurrences (all) | 1 | 1 | |
| Nausea | | | |
| subjects affected / exposed | 5 / 61 (8.20%) | 3 / 28 (10.71%) | |
| occurrences (all) | 6 | 3 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vomiting | | | |
| subjects affected / exposed | 9 / 61 (14.75%) | 5 / 28 (17.86%) | |
| occurrences (all) | 11 | 6 | |
| Colon dysplasia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences (all) | 0 | 1 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|--|----------------|----------------|--|
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences (all) | 0 | 1 | |
| Erythema | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 0 / 28 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Pruritus | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 0 / 28 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Psoriasis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash macular | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 28 (3.57%) | |
| occurrences (all) | 1 | 1 | |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences (all) | 0 | 3 | |
| Skin reaction | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences (all) | 0 | 1 | |
| Telangiectasia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 28 (3.57%) | |
| occurrences (all) | 1 | 1 | |
| Ingrown hair | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences (all) | 0 | 1 | |
| Renal failure | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 2 / 61 (3.28%) | 0 / 28 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Bladder disorder | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 1 / 28 (3.57%) | |
| occurrences (all) | 3 | 2 | |
| Back pain | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 28 (3.57%) | |
| occurrences (all) | 2 | 1 | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Flank pain | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Joint swelling | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 28 (3.57%) | |
| occurrences (all) | 1 | 1 | |
| Muscle spasms | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 2 / 28 (7.14%) | |
| occurrences (all) | 3 | 2 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 28 (3.57%) | |
| occurrences (all) | 1 | 1 | |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 1 / 28 (3.57%) | |
| occurrences (all) | 3 | 1 | |
| Pain in jaw | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 28 (3.57%) | |
| occurrences (all) | 1 | 1 | |
| Rheumatoid arthritis | | | |

| | | | |
|--------------------------------|----------------|-----------------|--|
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences (all) | 0 | 1 | |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 3 / 28 (10.71%) | |
| occurrences (all) | 2 | 3 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences (all) | 0 | 1 | |
| Ear infection | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) | |
| occurrences (all) | 0 | 1 | |
| Eye infection | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fungal skin infection | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | |
|-----------------------------------|-----------------|----------------|
| Gingivitis | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 1 |
| Laryngitis | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 |
| Lower respiratory tract infection | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 1 |
| Mastitis | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 |
| Nasopharyngitis | | |
| subjects affected / exposed | 9 / 61 (14.75%) | 1 / 28 (3.57%) |
| occurrences (all) | 11 | 1 |
| Sinusitis | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 |
| Upper respiratory tract infection | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 28 (3.57%) |
| occurrences (all) | 1 | 1 |
| Urinary tract infection | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 28 (3.57%) |
| occurrences (all) | 1 | 1 |
| Vulvovaginal candidiasis | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 1 |
| Pharyngotonsillitis | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 28 (0.00%) |
| occurrences (all) | 1 | 0 |
| Catheter site infection | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 3 |
| Post viral fatigue syndrome | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 0 | 1 |

| | | | |
|---|---------------------|---------------------|--|
| Respiratory tract infection viral subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 28 (3.57%) 1 | |
| Respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 28 (3.57%) 1 | |
| Puncture site infection subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 28 (3.57%) 1 | |
| Metabolism and nutrition disorders | | | |
| Dehydration subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 28 (0.00%) 0 | |
| Fluid overload subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 0 / 28 (0.00%) 0 | |
| Gout subjects affected / exposed occurrences (all) | 2 / 61 (3.28%) 2 | 0 / 28 (0.00%) 0 | |
| Hypercholesterolaemia subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 28 (3.57%) 1 | |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 2 | 0 / 28 (0.00%) 0 | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 4 / 61 (6.56%) 4 | 2 / 28 (7.14%) 2 | |
| Decreased appetite subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 1 / 28 (3.57%) 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 20 February 2014 | <p>Following modifications were done in this amendment:</p> <p>1: Changed sildenafil dose from 20 mg tid to 80 mg tid.</p> <p>2: Reduced washout period for sildenafil from 3 to 1 day. It stayed 3 days for tadalafil.</p> <p>3: Revised inclusion criteria:</p> <p>A. Subjects with associated PAH due to congenital heart disease were allowed to be enrolled.</p> <p>B. The upper limit for cardiac index as one of the criteria for insufficient response/not at treatment target was increased from <2.5 to <3.0 liter per minute per square meter (L/min/m²). Lower limit for pulmonary vascular resistance as an additional inclusion criterion was proportionally decreased from >480 to 400 dyne*second*centimeter⁻⁵.</p> <p>C. Age range widened to include subjects up to 75 years old.</p> <p>4: Following exclusion criteria revised:</p> <p>A -Moderate to severe bronchial asthma or chronic obstructive pulmonary disease and</p> <p>-Moderate to severe restrictive lung disease total lung capacity <70% predicted replaced with:</p> <p>-Evidence of clinically significant restrictive or obstructive parenchymal lung diseases in the judgment of the investigator (based on a clean computed tomography [CT] lung scan).</p> <p>B. The lower limit for diffusing capacity of lung for carbon monoxide as an exclusion criterion was decreased from 40 to 30% predicted.</p> <p>C. Previous treatment with riociguat was added as an exclusion criterion.</p> <p>5: Revised withdrawal criteria:</p> <p>Subject diagnosed with pulmonary veno-occlusive disease while on treatment with study drug the administration of riociguat had to be stopped immediately.</p> <p>6: Dose increase time during titration phase was increased to also allow increase at Visit 5 (Week 8).</p> <p>7: LPH questionnaire was removed from the study procedures.</p> <p>8: Corrected time periods definitions:</p> <p>Time periods of 3 months and 12 weeks were replaced by 90 days.</p> <p>9: Syncope as special interest AE was replaced by symptomatic hypotension and hemoptysis.</p> <p>10: Left atrial volume index was added as an additional echocardiogram parameter.</p> |

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|------------------|--|
| 27 February 2015 | <p>Following modifications were done in this amendment:</p> <p>Modification 1: Added interim analysis: An interim analysis was added to evaluate clinical monitoring signals on efficacy and/or safety, which would be presented to the advisory board to support continued enrollment in the study, because experience of switching from PDE-5i in this patient population is very limited.</p> <p>Modification 2: Added time window for prior PDE-5i therapy: Time window of 7 days was added to the period of 90 days for prior PDE-5i therapy, to better adapt to routine clinical practice and to allow for more flexibility.</p> <p>Modification 3: Change of the sponsor's medically responsible person: Sponsor's medically responsible person was changed; therefore the name was updated on the signature page.</p> <p>Modification 4: Other text/inconsistencies corrections: In addition to the changes specified above the protocol text was corrected for better clarity and consistency.</p> |
| 24 February 2016 | <p>Following modifications were done in this amendment:</p> <p>Modification 1. The definition of end of study and the time point for reporting was clarified. The time point for the clinical study report is the last visit of the last subject in the main phase (maintenance phase up to Visit 7 at Week 24 including the safety follow-up visit, if applicable). The extended drug supply phase is considered an extension of the study and will be reported as an addendum to the study report.</p> <p>Modification 2. Addition of transition to long-term extension study: The option was implemented for subjects to transition to a separate long-term extension study at the end of the maintenance phase or during the extended drug supply phase.</p> <p>Modification 3: Change of the sponsor's medically responsible person: Sponsor's medically responsible person was changed; therefore the name was updated on the signature page.</p> <p>Modification 4. Clarification of applicability of the safety follow-up visit: It was clarified that the safety follow-up visit is applicable only for subjects who terminate the treatment prematurely or formally complete treatment according to protocol at Visit 7. Subjects continuing treatment after Visit 7 without treatment interruption in the extended drug supply phase of the study or in a Bayer/ Merck Sharp & Dohme (MSD-sponsored) riociguat long-term extension study or any other extended access program for riociguat are not required to come in for the safety follow-up visit.</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.

Occurrence of "±" in relation with geometric CV is auto-generated and cannot be deleted. Decimal places were automatically truncated if last decimal equals zero.

Notes: