



## Clinical trial results:

**A prospective, randomized, international, multicenter, double arm, controlled, open label study of Riociguat in patients with pulmonary arterial hypertension (PAH) who are on a stable dose of phosphodiesterase 5 inhibitors (PDE 5i) with or without endothelin receptor antagonist (ERA), but not at treatment goal**

### Summary

|                          |                                     |
|--------------------------|-------------------------------------|
| EudraCT number           | 2016-001067-36                      |
| Trial protocol           | ES PT AT CZ GB DE BE NL DK GR PL IT |
| Global end of trial date | 02 March 2020                       |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 07 January 2021 |
| First version publication date | 07 January 2021 |

### Trial information

#### Trial identification

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | BAY63-2521/18588 |
|-----------------------|------------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02891850 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Bayer AG   |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368                 |
| Public contact               | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |
| Scientific contact           | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |               |
|--|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 16 April 2020 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 02 March 2020 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the proportion of subjects in each treatment arm with a satisfactory clinical response as defined by a composite primary endpoint at Week 24.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with 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 was read by and explained to all the 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                          | 10 January 2017 |
| 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: 20      |
| Country: Number of subjects enrolled | United Kingdom: 4      |
| Country: Number of subjects enrolled | Brazil: 42             |
| Country: Number of subjects enrolled | Canada: 1              |
| Country: Number of subjects enrolled | Czechia: 25            |
| Country: Number of subjects enrolled | Germany: 38            |
| Country: Number of subjects enrolled | Denmark: 1             |
| Country: Number of subjects enrolled | Spain: 9               |
| Country: Number of subjects enrolled | France: 3              |
| Country: Number of subjects enrolled | Greece: 4              |
| Country: Number of subjects enrolled | Italy: 12              |
| Country: Number of subjects enrolled | Japan: 4               |
| Country: Number of subjects enrolled | Korea, Republic of: 20 |
| Country: Number of subjects enrolled | Mexico: 15             |
| Country: Number of subjects enrolled | Netherlands: 2         |
| Country: Number of subjects enrolled | Portugal: 6            |
| Country: Number of subjects enrolled | Turkey: 8              |

|                                      |           |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Taiwan: 9 |
| Country: Number of subjects enrolled | Poland: 2 |
| Worldwide total number of subjects   | 225       |
| EEA total number of subjects         | 106       |

Notes:

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### 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)                      | 173 |
| From 65 to 84 years                       | 52  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Study was conducted at multiple centers in 21 countries between 11-JAN-2017 (first participant first visit) and 03-MAR-2020 (last participant last visit).

### Pre-assignment

Screening details:

293 participants were screened in this study. Of these, 67 participants did not enter the treatment period (60 screening failures; 2 withdraw during screening; 2 withdraw following physician decision; 3 withdraw due to other reasons). 226 participants were randomized, of which 1 participant withdraw before treated.

### Period 1

|                              |                          |
|------------------------------|--------------------------|
| Period 1 title               | Overall (overall period) |
| Is this the baseline period? | Yes                      |
| Allocation method            | Randomised - controlled  |
| Blinding used                | Not blinded              |

### Arms

|                              |           |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes       |
| <b>Arm title</b>             | Riociguat |

Arm description:

Participants received BAY63-2521 tablets at a dosage of 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg three times a day (TID) for 24 weeks, started with 1.0 mg TID, followed by a dose adjustment period of 8 weeks, then stayed at the optimal dose period of 16 weeks.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Adempas      |
| Investigational medicinal product code | BAY63-2521   |
| Other name                             | Adempas      |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg administered three times a day (TID) for 24 weeks, started with 1.0 mg TID, followed by a dose adjustment period of 8 weeks, then stayed at the optimal dose period of 16 weeks, tablets administrated orally

|                  |        |
|------------------|--------|
| <b>Arm title</b> | PDE-5i |
|------------------|--------|

Arm description:

Participants remained on their current pulmonary arterial hypertension (PAH) treatment on tadalafil (20 to 40 mg/day) or sildenafil (at least 60 mg/day) for 24 weeks at the discretion of the investigator.

|  |                    |
|--|--------------------|
| Arm type                               | Active comparator  |
| Investigational medicinal product name | Tadalafil          |
| Investigational medicinal product code |                    |
| Other name                             | ADCIRCA            |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

20 to 40 mg/day for 24 weeks as per the investigator's discretion, tablets administrated orally

|  |                    |
|--|--------------------|
| Investigational medicinal product name | Sildenafil citrate |
| Investigational medicinal product code |                    |
| Other name                             | REVATIO            |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

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**Dosage and administration details:**

At least 60 mg/day for 24 weeks as per the investigator's discretion, tablets administrated orally

| <b>Number of subjects in period 1</b> | Riociguat | PDE-5i |
|---------------------------------------|-----------|--------|
| Started                               | 111       | 114    |
| Completed                             | 104       | 107    |
| Not completed                         | 7         | 7      |
| Adverse event, serious fatal          | -         | 4      |
| Consent withdrawn by subject          | 2         | 3      |
| Physician decision                    | 1         | -      |
| Adverse event, non-fatal              | 3         | -      |
| Pregnancy                             | 1         | -      |

## Baseline characteristics

### Reporting groups

|  |           |
|--|-----------|
| Reporting group title  | Riociguat |
| Reporting group description:   |           |
| Participants received BAY63-2521 tablets at a dosage of 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg three times a day (TID) for 24 weeks, started with 1.0 mg TID, followed by a dose adjustment period of 8 weeks, then stayed at the optimal dose period of 16 weeks. |           |
| Reporting group title  | PDE-5i    |
| Reporting group description:   |           |
| Participants remained on their current pulmonary arterial hypertension (PAH) treatment on tadalafil (20 to 40 mg/day) or sildenafil (at least 60 mg/day) for 24 weeks at the discretion of the investigator.   |           |

| Reporting group values                    | Riociguat | PDE-5i  | Total |
|---|-----------|---------|-------|
| Number of subjects                        | 111       | 114     | 225   |
| Age Categorical<br>Units:                 |           |         |       |
| Age Continuous<br>Units: years            |           |         |       |
| arithmetic mean                           | 49.4      | 49.2    |       |
| standard deviation                        | ± 16.16   | ± 15.64 | -     |
| Gender Categorical<br>Units: participants |           |         |       |
| Female                                    | 82        | 95      | 177   |
| Male                                      | 29        | 19      | 48    |
| Race<br>Units: Subjects                   |           |         |       |
| White                                     | 86        | 89      | 175   |
| Black or African American                 | 4         | 5       | 9     |
| Asian                                     | 17        | 19      | 36    |
| American Indian or Alaska Native          | 1         | 0       | 1     |
| Not Reported                              | 3         | 1       | 4     |
| Ethnicity<br>Units: Subjects              |           |         |       |
| Hispanic or Latino                        | 32        | 31      | 63    |
| Not Hispanic or Latino                    | 75        | 80      | 155   |
| Not Reported                              | 4         | 3       | 7     |

## End points

### End points reporting groups

|  |                           |
|--|---------------------------|
| Reporting group title  | Riociguat                 |
| Reporting group description:<br>Participants received BAY63-2521 tablets at a dosage of 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg three times a day (TID) for 24 weeks, started with 1.0 mg TID, followed by a dose adjustment period of 8 weeks, then stayed at the optimal dose period of 16 weeks. |                           |
| Reporting group title  | PDE-5i                    |
| Reporting group description:<br>Participants remained on their current pulmonary arterial hypertension (PAH) treatment on tadalafil (20 to 40 mg/day) or sildenafil (at least 60 mg/day) for 24 weeks at the discretion of the investigator.   |                           |
| Subject analysis set title   | Full Analysis Set (FAS)   |
| Subject analysis set type  | Sub-group analysis        |
| Subject analysis set description:<br>The participants who were randomized and took at least 1 medication were considered for the FAS. Participants were analyzed as randomized.  |                           |
| Subject analysis set title   | Safety Analysis Set (SAF) |
| Subject analysis set type  | Safety analysis           |
| Subject analysis set description:<br>The population for safety analysis comprised all participants who received at least 1 dose of study drug. Participants in the SAF were analyzed as treated.   |                           |

### Primary: Number of Participants with Satisfactory Clinical Response at Week 24

|  |   |
|--|---|
| End point title  | Number of Participants with Satisfactory Clinical Response at Week 24 |
| End point description:<br>The treatment is assessed as efficient (participants with satisfactory clinical response) in case at least 2 out of the following 3 criteria were fulfilled<br><ul style="list-style-type: none"><li>• 6 Minute Walking Distance increase by <math>\geq 10\%</math> or <math>\geq 30</math> m from baseline to Week 24</li><li>• World Health Organization Functional Class (WHO FC) I or II at Week 24</li><li>• N-terminal pro-brain natriuretic peptide (NT-proBNP) reduction <math>\geq 30\%</math> from baseline to Week 24 (NT-proBNP ratio Week 24/baseline <math>\leq 0.7</math>)</li></ul> and<br>in absence of the defined criteria of clinical worsening. |   |
| End point type   | Primary   |
| End point timeframe:<br>At Week 24   |   |

| End point values                       | Riociguat          | PDE-5i             |  |  |
|--|--------------------|--------------------|--|--|
| Subject group type                     | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed            | 111 <sup>[1]</sup> | 113 <sup>[2]</sup> |  |  |
| Units: participants                    |                    |                    |  |  |
| With satisfactory clinical response    | 45                 | 23                 |  |  |
| Without satisfactory clinical response | 66                 | 90                 |  |  |

Notes:

[1] - Full Analysis Set (FAS) with evaluable participants

[2] - Full Analysis Set (FAS) with evaluable participants

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | OR for satisfactory clinical response at Week 24 |
| Comparison groups                       | PDE-5i v Riociguat                               |
| Number of subjects included in analysis | 224  |
| Analysis specification                  | Pre-specified                                    |
| Analysis type                           | equivalence <sup>[3]</sup>                       |
| P-value                                 | = 0.0007   |
| Method                                  | Mantel-Haenszel                                  |
| Parameter estimate                      | Odds ratio (OR)                                  |
| Point estimate                          | 2.78   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 1.526  |
| upper limit                             | 5.06   |

Notes:

[3] - Stratified by PAH category at baseline

### Secondary: Change in 6 Minute Walking Distance (6MWD) with Last Observation Carried Forward from baseline to 24 weeks

|                 |  |
|-----------------|--|
| End point title | Change in 6 Minute Walking Distance (6MWD) with Last Observation Carried Forward from baseline to 24 weeks |
|-----------------|--|

End point description:

Six-minute walk distance (6MWD) was conducted to test the physical limitations of the participant by assessing the participant's exercise capacity. The distance walked by the participant in 6 minutes was measured.

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

End point timeframe:

From baseline and up to 24 weeks

| End point values                     | Riociguat          | PDE-5i             |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 111 <sup>[4]</sup> | 113 <sup>[5]</sup> |  |  |
| Units: meters (m)                    |                    |                    |  |  |
| arithmetic mean (standard deviation) | 36.448 (± 65.9748) | 13.884 (± 67.1552) |  |  |

Notes:

[4] - Full Analysis Set (FAS) with evaluable participants

[5] - Full Analysis Set (FAS) with evaluable participants

### Statistical analyses

|                                   |                                    |
|-----------------------------------|------------------------------------|
| <b>Statistical analysis title</b> | Mean difference of 6MWD at Week 24 |
| Comparison groups                 | Riociguat v PDE-5i                 |



|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 224                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | equivalence <sup>[6]</sup>     |
| P-value                                 | = 0.0542                       |
| Method                                  | t-test, 2-sided                |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 22.56                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 5.03                           |
| upper limit                             | 40.1                           |

Notes:

[6] - Stratified by PAH category at baseline

### Secondary: Change in N-terminal Pro-Brain Natriuretic Peptide (NT-proBNP) with Last Observation Carried Forward at Week 24

|                        |   |
|------------------------|---|
| End point title        | Change in N-terminal Pro-Brain Natriuretic Peptide (NT-proBNP) with Last Observation Carried Forward at Week 24   |
| End point description: | N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in the blood are used for screening, diagnosis of acute congestive heart failure (CHF) and may be useful to establish prognosis in heart failure. |
| End point type         | Secondary   |
| End point timeframe:   | From baseline and up to 24 weeks  |

| End point values                        | Riociguat            | PDE-5i               |  |  |
|---|----------------------|----------------------|--|--|
| Subject group type                      | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed             | 108 <sup>[7]</sup>   | 113 <sup>[8]</sup>   |  |  |
| Units: picograms per milliliter (pg/mL) |                      |                      |  |  |
| arithmetic mean (standard deviation)    | -88.234 (± 533.9179) | 81.414 (± 1267.6142) |  |  |

Notes:

[7] - Full Analysis Set (FAS) with evaluable participants

[8] - Full Analysis Set (FAS) with evaluable participants

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | Mean difference of NT-proBNP at Week 24 |
| Comparison groups                       | Riociguat v PDE-5i                      |
| Number of subjects included in analysis | 221                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | equivalence <sup>[9]</sup>              |
| P-value                                 | = 0.1067                                |
| Method                                  | t-test, 2-sided                         |
| Parameter estimate                      | Mean difference (final values)          |
| Point estimate                          | -169.65                                 |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -426.18 |
| upper limit         | 86.88   |

Notes:

[9] - Stratified by PAH category at baseline

### Secondary: Change in World Health Organization Functional Class (WHO FC) with Last Observation Carried Forward at Week 24

|                 |  |
|-----------------|--|
| End point title | Change in World Health Organization Functional Class (WHO FC) with Last Observation Carried Forward at Week 24 |
|-----------------|--|

End point description:

The participant's functional class was determined by using the WHO classification. Possible classes range from I (patients with pulmonary hypertension (PH) but without resulting limitation of physical activity) to IV (patients with PH with inability to carry out any physical activity without symptoms).

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

End point timeframe:

From baseline and up to 24 weeks

| End point values                     | Riociguat           | PDE-5i              |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 111 <sup>[10]</sup> | 113 <sup>[11]</sup> |  |  |
| Units: class                         |                     |                     |  |  |
| arithmetic mean (standard deviation) | -0.5 (± 0.58)       | -0.2 (± 0.62)       |  |  |

Notes:

[10] - Full Analysis Set (FAS) with evaluable participants

[11] - Full Analysis Set (FAS) with evaluable participants

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Mean difference in WHO FC from baseline to Week 24 |
| Comparison groups                       | Riociguat v PDE-5i                                 |
| Number of subjects included in analysis | 224  |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | equivalence <sup>[12]</sup>                        |
| P-value                                 | = 0.0007   |
| Method                                  | t-test, 2-sided                                    |
| Parameter estimate                      | Mean difference (final values)                     |
| Point estimate                          | -0.26  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -0.42  |
| upper limit                             | -0.11  |

Notes:

[12] - Stratified by PAH category at baseline

### Secondary: Number of Participants with Adjudicated Clinical Worsening at Week 24

|  |   |
|--|---|
| End point title  | Number of Participants with Adjudicated Clinical Worsening at Week 24 |
| End point description:<br>Clinical worsening was defined as death of any cause, hospitalization due to worsening pulmonary arterial hypertension (PAH) (adjudicated) or disease progression (adjudicated). |   |
| End point type   | Secondary   |
| End point timeframe:<br>Up to 24 weeks   |   |

| End point values            | Riociguat           | PDE-5i              |  |  |
|-----------------------------|---------------------|---------------------|--|--|
| Subject group type          | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed | 111 <sup>[13]</sup> | 113 <sup>[14]</sup> |  |  |
| Units: participants         |                     |                     |  |  |
| Yes                         | 1                   | 10                  |  |  |

Notes:

[13] - Full Analysis Set (FAS) with evaluable participants

[14] - Full Analysis Set (FAS) with evaluable participants

### Statistical analyses

| Statistical analysis title              | OR for the clinical worsening at Week 24 |
|---|--|
| Comparison groups                       | Riociguat v PDE-5i                       |
| Number of subjects included in analysis | 224                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | equivalence <sup>[15]</sup>              |
| P-value                                 | = 0.0047                                 |
| Method                                  | Mantel-Haenszel                          |
| Parameter estimate                      | Odds ratio (OR)                          |
| Point estimate                          | 0.1                                      |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | 0.013                                    |
| upper limit                             | 0.725                                    |

Notes:

[15] - Stratified by PAH category at baseline

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The adverse events were considered to be treatment emergent if they had started or worsened after the first treatment administration up to 2 days after end of treatment.

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

### Dictionary used

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

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

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Riociguat |
|-----------------------|-----------|

Reporting group description:

Participants received riociguat/BAY63-2521 tablets at a dosage of 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg three times a day (TID) for 24 weeks, started with 1.0 mg TID, followed by a dose adjustment period of 8 weeks, then stayed at the optimal dose period of 16 weeks.

|                       |        |
|-----------------------|--------|
| Reporting group title | PDE-5i |
|-----------------------|--------|

Reporting group description:

Participants remained on their current pulmonary arterial hypertension (PAH) treatment on tadalafil (20 to 40 mg/day) or sildenafil (at least 60 mg/day) for 24 weeks at the discretion of the investigator.

| Serious adverse events                            | Riociguat       | PDE-5i            |  |
|---|-----------------|-------------------|--|
| Total subjects affected by serious adverse events |                 |                   |  |
| subjects affected / exposed                       | 8 / 111 (7.21%) | 19 / 114 (16.67%) |  |
| number of deaths (all causes)                     | 0               | 4                 |  |
| number of deaths resulting from adverse events    | 0               | 3                 |  |
| Investigations                                    |                 |                   |  |
| Pulmonary arterial pressure increased             |                 |                   |  |
| subjects affected / exposed                       | 0 / 111 (0.00%) | 1 / 114 (0.88%)   |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1             |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0             |  |
| Vascular disorders                                |                 |                   |  |
| Hypotension                                       |                 |                   |  |
| subjects affected / exposed                       | 2 / 111 (1.80%) | 0 / 114 (0.00%)   |  |
| occurrences causally related to treatment / all   | 3 / 3           | 0 / 0             |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0             |  |
| Cardiac disorders                                 |                 |                   |  |
| Arrhythmia supraventricular                       |                 |                   |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| 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                     | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                 |                 |                 |  |
| Drug therapy enhancement                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Epilepsy  |                 |                 |  |
| subjects affected / exposed                     | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope   |                 |                 |  |
| subjects affected / exposed                     | 1 / 111 (0.90%) | 1 / 114 (0.88%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Iron deficiency anaemia                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| 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 |                 |                 |  |
| Chest pain   |                 |                 |  |
| subjects affected / exposed                          | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                           |                 |                 |  |
| Gastrointestinal haemorrhage                         |                 |                 |  |
| subjects affected / exposed                          | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Small intestinal obstruction                         |                 |                 |  |
| subjects affected / exposed                          | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders      |                 |                 |  |
| Dyspnoea   |                 |                 |  |
| subjects affected / exposed                          | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Dyspnoea exertional                                  |                 |                 |  |
| subjects affected / exposed                          | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Epistaxis  |                 |                 |  |
| subjects affected / exposed                          | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Pulmonary hypertension                               |                 |                 |  |
| subjects affected / exposed                          | 0 / 111 (0.00%) | 2 / 114 (1.75%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 1           |  |
| Pulmonary arterial hypertension                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 111 (0.00%) | 2 / 114 (1.75%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Osteonecrosis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 111 (0.90%) | 0 / 114 (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                     |                 |                 |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 111 (0.00%) | 2 / 114 (1.75%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tracheobronchitis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Viral infection                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| 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 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |

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

| <b>Non-serious adverse events</b>                     | Riociguat         | PDE-5i            |  |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 77 / 111 (69.37%) | 72 / 114 (63.16%) |  |
| Vascular disorders                                    |                   |                   |  |
| Circulatory collapse                                  |                   |                   |  |
| subjects affected / exposed                           | 0 / 111 (0.00%)   | 1 / 114 (0.88%)   |  |
| occurrences (all)                                     | 0                 | 1                 |  |
| Flushing  |                   |                   |  |
| subjects affected / exposed                           | 1 / 111 (0.90%)   | 1 / 114 (0.88%)   |  |
| occurrences (all)                                     | 1                 | 1                 |  |
| Hypertension  |                   |                   |  |
| subjects affected / exposed                           | 0 / 111 (0.00%)   | 1 / 114 (0.88%)   |  |
| occurrences (all)                                     | 0                 | 1                 |  |
| Hypotension   |                   |                   |  |
| subjects affected / exposed                           | 13 / 111 (11.71%) | 6 / 114 (5.26%)   |  |
| occurrences (all)                                     | 19                | 11                |  |
| Orthostatic hypotension                               |                   |                   |  |
| subjects affected / exposed                           | 0 / 111 (0.00%)   | 1 / 114 (0.88%)   |  |
| occurrences (all)                                     | 0                 | 1                 |  |
| Jugular vein distension                               |                   |                   |  |
| subjects affected / exposed                           | 0 / 111 (0.00%)   | 1 / 114 (0.88%)   |  |
| occurrences (all)                                     | 0                 | 1                 |  |
| Surgical and medical procedures                       |                   |                   |  |
| Tooth extraction                                      |                   |                   |  |
| subjects affected / exposed                           | 0 / 111 (0.00%)   | 1 / 114 (0.88%)   |  |
| occurrences (all)                                     | 0                 | 1                 |  |
| General disorders and administration site conditions  |                   |                   |  |
| Asthenia  |                   |                   |  |
| subjects affected / exposed                           | 0 / 111 (0.00%)   | 2 / 114 (1.75%)   |  |
| occurrences (all)                                     | 0                 | 2                 |  |
| Chest discomfort                                      |                   |                   |  |



|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)           | 0               | 1               |  |
| Chest pain                  |                 |                 |  |
| subjects affected / exposed | 5 / 111 (4.50%) | 5 / 114 (4.39%) |  |
| occurrences (all)           | 8               | 5               |  |
| Drug ineffective            |                 |                 |  |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)           | 0               | 1               |  |
| Fatigue                     |                 |                 |  |
| subjects affected / exposed | 6 / 111 (5.41%) | 2 / 114 (1.75%) |  |
| occurrences (all)           | 7               | 2               |  |
| Malaise                     |                 |                 |  |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Oedema                      |                 |                 |  |
| subjects affected / exposed | 2 / 111 (1.80%) | 2 / 114 (1.75%) |  |
| occurrences (all)           | 2               | 2               |  |
| Oedema mucosal              |                 |                 |  |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Oedema peripheral           |                 |                 |  |
| subjects affected / exposed | 3 / 111 (2.70%) | 4 / 114 (3.51%) |  |
| occurrences (all)           | 4               | 4               |  |
| Pyrexia                     |                 |                 |  |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Peripheral swelling         |                 |                 |  |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)           | 0               | 1               |  |
| Immune system disorders     |                 |                 |  |
| Drug hypersensitivity       |                 |                 |  |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)           | 0               | 1               |  |
| Hypersensitivity            |                 |                 |  |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)           | 0               | 1               |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Reproductive system and breast disorders        |                 |                 |  |
| Dysmenorrhoea                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Menometrorrhagia                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Adnexa uteri cyst                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Asthma  |                 |                 |  |
| subjects affected / exposed                     | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Cough   |                 |                 |  |
| subjects affected / exposed                     | 0 / 111 (0.00%) | 7 / 114 (6.14%) |  |
| occurrences (all)                               | 0               | 7               |  |
| Dry throat                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                     | 3 / 111 (2.70%) | 5 / 114 (4.39%) |  |
| occurrences (all)                               | 4               | 6               |  |
| Dyspnoea exertional                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 111 (1.80%) | 0 / 114 (0.00%) |  |
| occurrences (all)                               | 3               | 0               |  |
| Epistaxis                                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 111 (2.70%) | 3 / 114 (2.63%) |  |
| occurrences (all)                               | 3               | 4               |  |
| Hypoxia   |                 |                 |  |
| subjects affected / exposed                     | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Lung disorder                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Nasal congestion                                |                 |                 |  |

|                                 |                 |                 |
|---------------------------------|-----------------|-----------------|
| subjects affected / exposed     | 1 / 111 (0.90%) | 1 / 114 (0.88%) |
| occurrences (all)               | 1               | 1               |
| Nasal polyps                    |                 |                 |
| subjects affected / exposed     | 1 / 111 (0.90%) | 0 / 114 (0.00%) |
| occurrences (all)               | 1               | 0               |
| Productive cough                |                 |                 |
| subjects affected / exposed     | 0 / 111 (0.00%) | 1 / 114 (0.88%) |
| occurrences (all)               | 0               | 1               |
| Pulmonary embolism              |                 |                 |
| subjects affected / exposed     | 0 / 111 (0.00%) | 1 / 114 (0.88%) |
| occurrences (all)               | 0               | 1               |
| Pulmonary hypertension          |                 |                 |
| subjects affected / exposed     | 0 / 111 (0.00%) | 1 / 114 (0.88%) |
| occurrences (all)               | 0               | 1               |
| Pulmonary oedema                |                 |                 |
| subjects affected / exposed     | 1 / 111 (0.90%) | 0 / 114 (0.00%) |
| occurrences (all)               | 1               | 0               |
| Rhinitis allergic               |                 |                 |
| subjects affected / exposed     | 2 / 111 (1.80%) | 0 / 114 (0.00%) |
| occurrences (all)               | 2               | 0               |
| Rhinorrhoea                     |                 |                 |
| subjects affected / exposed     | 1 / 111 (0.90%) | 0 / 114 (0.00%) |
| occurrences (all)               | 1               | 0               |
| Sleep apnoea syndrome           |                 |                 |
| subjects affected / exposed     | 1 / 111 (0.90%) | 0 / 114 (0.00%) |
| occurrences (all)               | 1               | 0               |
| Throat irritation               |                 |                 |
| subjects affected / exposed     | 0 / 111 (0.00%) | 1 / 114 (0.88%) |
| occurrences (all)               | 0               | 1               |
| Paranasal sinus hypersecretion  |                 |                 |
| subjects affected / exposed     | 1 / 111 (0.90%) | 0 / 114 (0.00%) |
| occurrences (all)               | 1               | 0               |
| Pulmonary arterial hypertension |                 |                 |
| subjects affected / exposed     | 0 / 111 (0.00%) | 1 / 114 (0.88%) |
| occurrences (all)               | 0               | 1               |
| Bronchial hyperreactivity       |                 |                 |

|                                   |                 |                 |  |
|-----------------------------------|-----------------|-----------------|--|
| subjects affected / exposed       | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)                 | 0               | 1               |  |
| Oropharyngeal pain                |                 |                 |  |
| subjects affected / exposed       | 0 / 111 (0.00%) | 2 / 114 (1.75%) |  |
| occurrences (all)                 | 0               | 2               |  |
| Psychiatric disorders             |                 |                 |  |
| Anxiety                           |                 |                 |  |
| subjects affected / exposed       | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)                 | 0               | 3               |  |
| Depression                        |                 |                 |  |
| subjects affected / exposed       | 2 / 111 (1.80%) | 0 / 114 (0.00%) |  |
| occurrences (all)                 | 2               | 0               |  |
| Insomnia                          |                 |                 |  |
| subjects affected / exposed       | 0 / 111 (0.00%) | 3 / 114 (2.63%) |  |
| occurrences (all)                 | 0               | 3               |  |
| Sleep disorder                    |                 |                 |  |
| subjects affected / exposed       | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)                 | 0               | 1               |  |
| Stress                            |                 |                 |  |
| subjects affected / exposed       | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences (all)                 | 1               | 0               |  |
| Investigations                    |                 |                 |  |
| Blood pressure decreased          |                 |                 |  |
| subjects affected / exposed       | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences (all)                 | 1               | 0               |  |
| Blood pressure systolic increased |                 |                 |  |
| subjects affected / exposed       | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)                 | 0               | 1               |  |
| Catheterisation cardiac           |                 |                 |  |
| subjects affected / exposed       | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences (all)                 | 1               | 0               |  |
| Haemoglobin decreased             |                 |                 |  |
| subjects affected / exposed       | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)                 | 0               | 1               |  |
| Prothrombin time prolonged        |                 |                 |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 111 (0.00%)<br>0 | 1 / 114 (0.88%)<br>1 |  |
| Hepatic enzyme increased<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 111 (0.90%)<br>1 | 0 / 114 (0.00%)<br>0 |  |
| N-terminal prohormone brain<br>natriuretic peptide increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 111 (0.00%)<br>0 | 1 / 114 (0.88%)<br>1 |  |
| Injury, poisoning and procedural<br>complications  |                      |                      |  |
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 111 (0.90%)<br>1 | 0 / 114 (0.00%)<br>0 |  |
| Muscle strain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 111 (0.00%)<br>0 | 1 / 114 (0.88%)<br>1 |  |
| Limb injury<br>subjects affected / exposed<br>occurrences (all)  | 1 / 111 (0.90%)<br>1 | 0 / 114 (0.00%)<br>0 |  |
| Bone contusion<br>subjects affected / exposed<br>occurrences (all)   | 1 / 111 (0.90%)<br>1 | 1 / 114 (0.88%)<br>1 |  |
| Cardiac disorders  |                      |                      |  |
| Arrhythmia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 111 (0.00%)<br>0 | 1 / 114 (0.88%)<br>1 |  |
| Atrial fibrillation<br>subjects affected / exposed<br>occurrences (all)  | 0 / 111 (0.00%)<br>0 | 1 / 114 (0.88%)<br>1 |  |
| Cardiac failure chronic<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 111 (0.90%)<br>1 | 0 / 114 (0.00%)<br>0 |  |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)   | 3 / 111 (2.70%)<br>4 | 4 / 114 (3.51%)<br>4 |  |
| Sinus tachycardia  |                      |                      |  |

|                                      |                   |                 |  |
|--------------------------------------|-------------------|-----------------|--|
| subjects affected / exposed          | 1 / 111 (0.90%)   | 0 / 114 (0.00%) |  |
| occurrences (all)                    | 1                 | 0               |  |
| Tachycardia                          |                   |                 |  |
| subjects affected / exposed          | 1 / 111 (0.90%)   | 0 / 114 (0.00%) |  |
| occurrences (all)                    | 1                 | 0               |  |
| Ventricular extrasystoles            |                   |                 |  |
| subjects affected / exposed          | 0 / 111 (0.00%)   | 2 / 114 (1.75%) |  |
| occurrences (all)                    | 0                 | 2               |  |
| Nervous system disorders             |                   |                 |  |
| Diabetic neuropathy                  |                   |                 |  |
| subjects affected / exposed          | 1 / 111 (0.90%)   | 0 / 114 (0.00%) |  |
| occurrences (all)                    | 1                 | 0               |  |
| Dizziness                            |                   |                 |  |
| subjects affected / exposed          | 5 / 111 (4.50%)   | 2 / 114 (1.75%) |  |
| occurrences (all)                    | 5                 | 2               |  |
| Headache                             |                   |                 |  |
| subjects affected / exposed          | 14 / 111 (12.61%) | 8 / 114 (7.02%) |  |
| occurrences (all)                    | 16                | 8               |  |
| Hypoaesthesia                        |                   |                 |  |
| subjects affected / exposed          | 1 / 111 (0.90%)   | 0 / 114 (0.00%) |  |
| occurrences (all)                    | 1                 | 0               |  |
| Migraine                             |                   |                 |  |
| subjects affected / exposed          | 1 / 111 (0.90%)   | 0 / 114 (0.00%) |  |
| occurrences (all)                    | 1                 | 0               |  |
| Presyncope                           |                   |                 |  |
| subjects affected / exposed          | 1 / 111 (0.90%)   | 2 / 114 (1.75%) |  |
| occurrences (all)                    | 1                 | 2               |  |
| Syncope                              |                   |                 |  |
| subjects affected / exposed          | 0 / 111 (0.00%)   | 2 / 114 (1.75%) |  |
| occurrences (all)                    | 0                 | 2               |  |
| Blood and lymphatic system disorders |                   |                 |  |
| Anaemia                              |                   |                 |  |
| subjects affected / exposed          | 0 / 111 (0.00%)   | 1 / 114 (0.88%) |  |
| occurrences (all)                    | 0                 | 1               |  |
| Anaemia megaloblastic                |                   |                 |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)           | 0               | 1               |  |
| Iron deficiency anaemia     |                 |                 |  |
| subjects affected / exposed | 2 / 111 (1.80%) | 0 / 114 (0.00%) |  |
| occurrences (all)           | 2               | 0               |  |
| Leukopenia                  |                 |                 |  |
| subjects affected / exposed | 0 / 111 (0.00%) | 2 / 114 (1.75%) |  |
| occurrences (all)           | 0               | 2               |  |
| Lymphopenia                 |                 |                 |  |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)           | 0               | 1               |  |
| Neutropenia                 |                 |                 |  |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)           | 0               | 1               |  |
| Ear and labyrinth disorders |                 |                 |  |
| Vertigo                     |                 |                 |  |
| subjects affected / exposed | 2 / 111 (1.80%) | 0 / 114 (0.00%) |  |
| occurrences (all)           | 3               | 0               |  |
| Eye disorders               |                 |                 |  |
| Astigmatism                 |                 |                 |  |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Cataract                    |                 |                 |  |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)           | 0               | 1               |  |
| Eye irritation              |                 |                 |  |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)           | 0               | 1               |  |
| Glaucoma                    |                 |                 |  |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Retinal disorder            |                 |                 |  |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Ocular discomfort           |                 |                 |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 111 (0.00%)<br>0 | 1 / 114 (0.88%)<br>1 |  |
| Gastrointestinal disorders                       |                      |                      |  |
| Abdominal discomfort                             |                      |                      |  |
| subjects affected / exposed                      | 3 / 111 (2.70%)      | 0 / 114 (0.00%)      |  |
| occurrences (all)                                | 3                    | 0                    |  |
| Abdominal distension                             |                      |                      |  |
| subjects affected / exposed                      | 0 / 111 (0.00%)      | 1 / 114 (0.88%)      |  |
| occurrences (all)                                | 0                    | 1                    |  |
| Abdominal pain                                   |                      |                      |  |
| subjects affected / exposed                      | 3 / 111 (2.70%)      | 0 / 114 (0.00%)      |  |
| occurrences (all)                                | 3                    | 0                    |  |
| Abdominal pain lower                             |                      |                      |  |
| subjects affected / exposed                      | 0 / 111 (0.00%)      | 1 / 114 (0.88%)      |  |
| occurrences (all)                                | 0                    | 1                    |  |
| Abdominal pain upper                             |                      |                      |  |
| subjects affected / exposed                      | 3 / 111 (2.70%)      | 1 / 114 (0.88%)      |  |
| occurrences (all)                                | 3                    | 1                    |  |
| Constipation                                     |                      |                      |  |
| subjects affected / exposed                      | 4 / 111 (3.60%)      | 0 / 114 (0.00%)      |  |
| occurrences (all)                                | 5                    | 0                    |  |
| Diarrhoea  |                      |                      |  |
| subjects affected / exposed                      | 6 / 111 (5.41%)      | 3 / 114 (2.63%)      |  |
| occurrences (all)                                | 6                    | 3                    |  |
| Dyspepsia  |                      |                      |  |
| subjects affected / exposed                      | 10 / 111 (9.01%)     | 0 / 114 (0.00%)      |  |
| occurrences (all)                                | 10                   | 0                    |  |
| Flatulence                                       |                      |                      |  |
| subjects affected / exposed                      | 1 / 111 (0.90%)      | 0 / 114 (0.00%)      |  |
| occurrences (all)                                | 1                    | 0                    |  |
| Gastritis  |                      |                      |  |
| subjects affected / exposed                      | 0 / 111 (0.00%)      | 1 / 114 (0.88%)      |  |
| occurrences (all)                                | 0                    | 1                    |  |
| Gastrooesophageal reflux disease                 |                      |                      |  |
| subjects affected / exposed                      | 8 / 111 (7.21%)      | 1 / 114 (0.88%)      |  |
| occurrences (all)                                | 10                   | 1                    |  |



|  |                      |                      |  |
|--|----------------------|----------------------|--|
| Gingival hypertrophy<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 111 (0.90%)<br>1 | 0 / 114 (0.00%)<br>0 |  |
| Irritable bowel syndrome<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 111 (0.00%)<br>0 | 1 / 114 (0.88%)<br>1 |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 5 / 111 (4.50%)<br>6 | 3 / 114 (2.63%)<br>3 |  |
| Toothache<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 111 (0.00%)<br>0 | 2 / 114 (1.75%)<br>2 |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                       | 3 / 111 (2.70%)<br>3 | 0 / 114 (0.00%)<br>0 |  |
| Gastrointestinal hypermotility<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 111 (0.90%)<br>1 | 0 / 114 (0.00%)<br>0 |  |
| Reflux gastritis<br>subjects affected / exposed<br>occurrences (all)                               | 1 / 111 (0.90%)<br>1 | 0 / 114 (0.00%)<br>0 |  |
| Hepatobiliary disorders<br>Hepatomegaly<br>subjects affected / exposed<br>occurrences (all)        | 0 / 111 (0.00%)<br>0 | 1 / 114 (0.88%)<br>1 |  |
| Skin and subcutaneous tissue disorders<br>Acne<br>subjects affected / exposed<br>occurrences (all) | 0 / 111 (0.00%)<br>0 | 1 / 114 (0.88%)<br>1 |  |
| Erythema<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 111 (0.90%)<br>1 | 0 / 114 (0.00%)<br>0 |  |
| Hyperhidrosis<br>subjects affected / exposed<br>occurrences (all)                                  | 1 / 111 (0.90%)<br>1 | 1 / 114 (0.88%)<br>1 |  |
| Pruritus   |                      |                      |  |

|   |                      |                      |  |
|---|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 0 / 111 (0.00%)<br>0 | 1 / 114 (0.88%)<br>1 |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)  | 0 / 111 (0.00%)<br>0 | 1 / 114 (0.88%)<br>1 |  |
| Renal and urinary disorders<br>Polyuria<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 111 (0.00%)<br>0 | 1 / 114 (0.88%)<br>1 |  |
| Urinary incontinence<br>subjects affected / exposed<br>occurrences (all)  | 0 / 111 (0.00%)<br>0 | 1 / 114 (0.88%)<br>1 |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 1 / 111 (0.90%)<br>1 | 3 / 114 (2.63%)<br>3 |  |
| Arthritis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 111 (0.00%)<br>0 | 1 / 114 (0.88%)<br>1 |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 1 / 111 (0.90%)<br>1 | 6 / 114 (5.26%)<br>6 |  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)   | 2 / 111 (1.80%)<br>2 | 1 / 114 (0.88%)<br>1 |  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 111 (0.00%)<br>0 | 1 / 114 (0.88%)<br>1 |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 111 (0.90%)<br>1 | 1 / 114 (0.88%)<br>1 |  |
| Neck pain<br>subjects affected / exposed<br>occurrences (all)   | 2 / 111 (1.80%)<br>2 | 1 / 114 (0.88%)<br>1 |  |
| Pain in extremity   |                      |                      |  |

|                                |                 |                 |  |
|--------------------------------|-----------------|-----------------|--|
| subjects affected / exposed    | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)              | 0               | 2               |  |
| Pain in jaw                    |                 |                 |  |
| subjects affected / exposed    | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences (all)              | 1               | 0               |  |
| Spinal osteoarthritis          |                 |                 |  |
| subjects affected / exposed    | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)              | 0               | 1               |  |
| Systemic lupus erythematosus   |                 |                 |  |
| subjects affected / exposed    | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences (all)              | 1               | 0               |  |
| Intervertebral disc protrusion |                 |                 |  |
| subjects affected / exposed    | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)              | 0               | 1               |  |
| Infections and infestations    |                 |                 |  |
| Acute sinusitis                |                 |                 |  |
| subjects affected / exposed    | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)              | 0               | 1               |  |
| Body tinea                     |                 |                 |  |
| subjects affected / exposed    | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences (all)              | 1               | 0               |  |
| Bronchitis                     |                 |                 |  |
| subjects affected / exposed    | 1 / 111 (0.90%) | 2 / 114 (1.75%) |  |
| occurrences (all)              | 1               | 2               |  |
| Conjunctivitis                 |                 |                 |  |
| subjects affected / exposed    | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)              | 0               | 1               |  |
| Diverticulitis                 |                 |                 |  |
| subjects affected / exposed    | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)              | 0               | 1               |  |
| Enterobiasis                   |                 |                 |  |
| subjects affected / exposed    | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences (all)              | 1               | 0               |  |
| Eye infection                  |                 |                 |  |
| subjects affected / exposed    | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)              | 0               | 1               |  |

|                                   |                 |                 |
|-----------------------------------|-----------------|-----------------|
| Fungal infection                  |                 |                 |
| subjects affected / exposed       | 1 / 111 (0.90%) | 0 / 114 (0.00%) |
| occurrences (all)                 | 1               | 0               |
| Gastroenteritis                   |                 |                 |
| subjects affected / exposed       | 1 / 111 (0.90%) | 0 / 114 (0.00%) |
| occurrences (all)                 | 1               | 0               |
| Hepatitis E                       |                 |                 |
| subjects affected / exposed       | 1 / 111 (0.90%) | 0 / 114 (0.00%) |
| occurrences (all)                 | 1               | 0               |
| Herpes zoster                     |                 |                 |
| subjects affected / exposed       | 1 / 111 (0.90%) | 0 / 114 (0.00%) |
| occurrences (all)                 | 1               | 0               |
| Influenza                         |                 |                 |
| subjects affected / exposed       | 1 / 111 (0.90%) | 2 / 114 (1.75%) |
| occurrences (all)                 | 1               | 2               |
| Laryngitis                        |                 |                 |
| subjects affected / exposed       | 0 / 111 (0.00%) | 2 / 114 (1.75%) |
| occurrences (all)                 | 0               | 2               |
| Lower respiratory tract infection |                 |                 |
| subjects affected / exposed       | 0 / 111 (0.00%) | 1 / 114 (0.88%) |
| occurrences (all)                 | 0               | 1               |
| Nasopharyngitis                   |                 |                 |
| subjects affected / exposed       | 8 / 111 (7.21%) | 5 / 114 (4.39%) |
| occurrences (all)                 | 8               | 5               |
| Otitis media                      |                 |                 |
| subjects affected / exposed       | 0 / 111 (0.00%) | 1 / 114 (0.88%) |
| occurrences (all)                 | 0               | 1               |
| Pneumonia                         |                 |                 |
| subjects affected / exposed       | 2 / 111 (1.80%) | 1 / 114 (0.88%) |
| occurrences (all)                 | 2               | 1               |
| Rhinitis                          |                 |                 |
| subjects affected / exposed       | 0 / 111 (0.00%) | 4 / 114 (3.51%) |
| occurrences (all)                 | 0               | 4               |
| Sinusitis                         |                 |                 |
| subjects affected / exposed       | 2 / 111 (1.80%) | 6 / 114 (5.26%) |
| occurrences (all)                 | 2               | 8               |

|                                    |                 |                 |  |
|------------------------------------|-----------------|-----------------|--|
| Tonsillitis                        |                 |                 |  |
| subjects affected / exposed        | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)                  | 0               | 1               |  |
| Upper respiratory tract infection  |                 |                 |  |
| subjects affected / exposed        | 4 / 111 (3.60%) | 7 / 114 (6.14%) |  |
| occurrences (all)                  | 4               | 8               |  |
| Urinary tract infection            |                 |                 |  |
| subjects affected / exposed        | 2 / 111 (1.80%) | 3 / 114 (2.63%) |  |
| occurrences (all)                  | 2               | 3               |  |
| Viral infection                    |                 |                 |  |
| subjects affected / exposed        | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences (all)                  | 1               | 0               |  |
| Pharyngotonsillitis                |                 |                 |  |
| subjects affected / exposed        | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences (all)                  | 1               | 0               |  |
| Febrile infection                  |                 |                 |  |
| subjects affected / exposed        | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)                  | 0               | 1               |  |
| Bronchitis viral                   |                 |                 |  |
| subjects affected / exposed        | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)                  | 0               | 1               |  |
| Mycobacterial infection            |                 |                 |  |
| subjects affected / exposed        | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)                  | 0               | 1               |  |
| Respiratory tract infection        |                 |                 |  |
| subjects affected / exposed        | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences (all)                  | 2               | 0               |  |
| Metabolism and nutrition disorders |                 |                 |  |
| Dehydration                        |                 |                 |  |
| subjects affected / exposed        | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)                  | 0               | 1               |  |
| Fluid retention                    |                 |                 |  |
| subjects affected / exposed        | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences (all)                  | 1               | 0               |  |
| Gout                               |                 |                 |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)           | 0               | 1               |  |
| Hyperuricaemia              |                 |                 |  |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)           | 0               | 1               |  |
| Hypokalaemia                |                 |                 |  |
| subjects affected / exposed | 0 / 111 (0.00%) | 4 / 114 (3.51%) |  |
| occurrences (all)           | 0               | 4               |  |
| Iron deficiency             |                 |                 |  |
| subjects affected / exposed | 2 / 111 (1.80%) | 4 / 114 (3.51%) |  |
| occurrences (all)           | 2               | 4               |  |
| Decreased appetite          |                 |                 |  |
| subjects affected / exposed | 1 / 111 (0.90%) | 0 / 114 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Type 2 diabetes mellitus    |                 |                 |  |
| subjects affected / exposed | 0 / 111 (0.00%) | 1 / 114 (0.88%) |  |
| occurrences (all)           | 0               | 1               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 05 January 2017 | Amendment 4 specified following modifications: 1. Any escalation of PAH therapy including targeted PAH drug was permitted during the study at the discretion of the investigator for the individual subject (independent from and without counting as clinical worsening) in both treatment arms. 2. To reiterate that the benefit risk balance for the population in this study (i.e. PAH, Dana Point Group 1) was positive, despite the potential safety issue in Study 13605 in subjects with pulmonary hypertension associated with idiopathic interstitial pneumonia (Dana Point Group 3) which had led to its early termination. 3. To add the requirement for adequate use of effective contraceptive methods during this study. 4. To include other biomarkers (in addition to NT proBNP), at the request of the advisory committee, to further elucidate the value of selected nitric oxide pathway related biomarkers for treatment decision in this controlled study and in comparison with biomarker results from the previous, uncontrolled RESPITE study. 5. To include details for consistency with the Company Core Data Sheet (e.g. titration rules) and other studies using riociguat (e.g. extending the time for collecting AE information). 6. Subjects with "confirmed obstructive sleep apnea" (Exclusion criterion 13f) was changed to "clinically significant obstructive sleep apnea", if not effectively treated for at least 90 days; only in US/Canada. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported