



## Clinical trial results:

**A multicenter, non-randomized, non-blinded, non-controlled study to investigate the impact of multiple doses of BAY 63-2521 on safety, tolerability, pharmacokinetics, and pharmacodynamics in patients with pulmonary hypertension in a 12 week 3 times a day individual dose titration scheme**

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

## Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2006-003520-10    |
| Trial protocol           | DE                |
| Global end of trial date | 12 September 2014 |

## Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1           |
| This version publication date  | 23 June 2016 |
| First version publication date | 23 June 2016 |

## Trial information

### Trial identification

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | BAY63-2521/12166 |
|-----------------------|------------------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00454558 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Bayer HealthCare AG   |
| Sponsor organisation address | Kaiser Wilhelm Allee, D-51368 Leverkusen, Germany,                                      |
| Public contact               | Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com |
| Scientific contact           | Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.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                       | 12 September 2014 |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 12 September 2014 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

To investigate the safety, tolerability, and feasibility of individual titration of riociguat according to peripheral systolic blood pressure. In addition, long-term safety and tolerability of riociguat were investigated during the optional open-label extension period.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Before entering the extension part of this study, the subject had to sign an additional informed consent form. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug. Before entering the extension part of this study, the subject had to sign an additional informed consent form.

Background therapy:

Basic pulmonary hypertension medications such as diuretics, oral anticoagulants, digitalis, calcium channel blockers given up to the approved dose in arterial hypertension, and oxygen supplementation, as well as an extended basic therapy with oral bosentan were allowed.

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 12 February 2007 |
| 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 | Germany: 75 |
| Worldwide total number of subjects   | 75          |
| EEA total number of subjects         | 75          |

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          | 0 |

|                           |    |
|---------------------------|----|
| months)                   |    |
| Children (2-11 years)     | 0  |
| Adolescents (12-17 years) | 0  |
| Adults (18-64 years)      | 42 |
| From 65 to 84 years       | 33 |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 16 centres in Germany between 12 February 2007 (first subject first visit) and 29 July 2014 (last subject last visit).

### Pre-assignment

Screening details:

Of the 78 subjects enrolled in the main study, 3 were screening failures. A total of 75 subjects received study drug and valid for the safety analysis in the main study, 3 prematurely discontinued study drug treatment due to adverse events. Only 68 subjects participated in the optional open-label extension period after Day 84 of the main study.

### Period 1

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

### Arms

|           |  |
|-----------|--|
| Arm title | Riociguat (Adempas, BAY63-2521) Main Study |
|-----------|--|

Arm description:

Subjects received Riociguat (Adempas, BAY63-2521) immediate release (IR) tablets with biweekly titrations of doses starting from 1.0 milligram (mg) thrice in a day (TID) up to 2.5 mg TID in steps of plus (+) 0.5 mg according to safety and tolerability (mainly peripheral systolic blood pressure) for 12 weeks.

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

Dosage and administration details:

Subjects received Riociguat (Adempas, BAY63-2521) IR tablets with biweekly titrations of doses starting from 1.0 mg TID up to 2.5 mg TID in steps of +0.5 mg according to safety and tolerability (mainly peripheral systolic blood pressure) for 12 weeks.

|                                       |  |
|---------------------------------------|--|
| <b>Number of subjects in period 1</b> | Riociguat (Adempas, BAY63-2521) Main Study |
| Started                               | 75   |
| Completed                             | 72   |
| Not completed                         | 3  |
| Adverse event                         | 3  |

**Period 2**

|                              |                                 |
|------------------------------|---------------------------------|
| Period 2 title               | Long-term Extension (LTE) Phase |
| Is this the baseline period? | No                              |
| Allocation method            | Not applicable                  |
| Blinding used                | Not blinded                     |

**Arms**

|                  |   |
|------------------|---|
| <b>Arm title</b> | Riociguat (Adempas, BAY63-2521) LTE Phase |
|------------------|---|

## Arm description:

Subjects who were willing to continue, entered the optional 84-month LTE phase until the premature termination of product development or until official approval and commercial availability of BAY63-2521 at a minimum dose of 0.5 mg TID and maximum dose of 2.5 mg TID.

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

## Dosage and administration details:

Subjects who were willing to continue, entered the optional 84month LTE phase until the premature termination of product development or until official approval and commercial availability of BAY63-2521 at a minimum dose of 0.5 mg TID and maximum dose of 2.5 mg TID.

|  |   |
|--|---|
| <b>Number of subjects in period 2</b>      | Riociguat (Adempas, BAY63-2521) LTE Phase |
| Started                                    | 68  |
| Completed                                  | 36  |
| Not completed                              | 32  |
| Consent withdrawn by subject               | 4   |
| Insufficient therapeutic effect            | 1   |
| Non-compliant with study drug              | 1   |
| Death                                      | 11  |
| Adverse event                              | 6   |
| Lost to follow-up                          | 1   |
| Investigator decision, not protocol driven | 8   |

## Baseline characteristics

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Riociguat (Adempas, BAY63-2521) Main Study |
|-----------------------|--|

Reporting group description:

Subjects received Riociguat (Adempas, BAY63-2521) immediate release (IR) tablets with biweekly titrations of doses starting from 1.0 milligram (mg) thrice in a day (TID) up to 2.5 mg TID in steps of plus (+) 0.5 mg according to safety and tolerability (mainly peripheral systolic blood pressure) for 12 weeks.

| Reporting group values  | Riociguat (Adempas, BAY63-2521) Main Study | Total |  |
|---|--|-------|--|
| Number of subjects  | 75   | 75    |  |
| Age Categorical<br>Units: Subjects                                      |  |       |  |
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 60.3<br>± 11.8                             | -     |  |
| Gender Categorical<br>Units: Subjects                                   |  |       |  |
| Female  | 41   | 41    |  |
| Male  | 34   | 34    |  |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | Riociguat (Adempas, BAY63-2521) Main Study                 |
| Reporting group description:<br>Subjects received Riociguat (Adempas, BAY63-2521) immediate release (IR) tablets with biweekly titrations of doses starting from 1.0 milligram (mg) thrice in a day (TID) up to 2.5 mg TID in steps of plus (+) 0.5 mg according to safety and tolerability (mainly peripheral systolic blood pressure) for 12 weeks. |  |
| Reporting group title   | Riociguat (Adempas, BAY63-2521) LTE Phase                  |
| Reporting group description:<br>Subjects who were willing to continue, entered the optional 84-month LTE phase until the premature termination of product development or until official approval and commercial availability of BAY63-2521 at a minimum dose of 0.5 mg TID and maximum dose of 2.5 mg TID.  |  |
| Subject analysis set title  | Safety set (Main Study)                                    |
| Subject analysis set type   | Safety analysis  |
| Subject analysis set description:<br>Safety set (N=75) included all subjects who received 1 dose of the study drug in the main study.   |  |
| Subject analysis set title  | Pharmacokinetic (PK)/Pharmacodynamic (PD) set (Main Study) |
| Subject analysis set type   | Per protocol   |
| Subject analysis set description:<br>PK/PD set (N=72) included all subjects who completed the 12-week treatment without major changes versus protocol in the main study.  |  |

### Primary: Number of Subjects With Systolic Blood Pressure Less Than 90 Millimeter of Mercury in the Long-term Extension Phase

|  |  |
|--|--|
| End point title  | Number of Subjects With Systolic Blood Pressure Less Than 90 Millimeter of Mercury in the Long-term Extension Phase <sup>[1]</sup> |
| End point description:   |  |
| End point type   | Primary  |
| End point timeframe:<br>From Day 84 (end of main study) until up to 7.25 years (87 months) of the 84-month LTE |  |

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: Descriptive statistics were done and inferential statistics were not planned as this is an open, single-group study.

|                             |   |  |  |  |
|-----------------------------|---|--|--|--|
| <b>End point values</b>     | Riociguat (Adempas, BAY63-2521) LTE Phase |  |  |  |
| Subject group type          | Reporting group                           |  |  |  |
| Number of subjects analysed | 68 <sup>[2]</sup>                         |  |  |  |
| Units: Subjects             | 16  |  |  |  |

Notes:

[2] - All subjects who entered the LTE phase.

### Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Treatment-emergent Adverse Events Related to

## Heart Rate and Blood Pressure in the Main Study

|                 |   |
|-----------------|---|
| End point title | Number of Subjects With Treatment-emergent Adverse Events Related to Heart Rate and Blood Pressure in the Main Study <sup>[3]</sup> |
|-----------------|---|

End point description:

An adverse event (AE) is any untoward medical occurrence (that is, any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Treatment-emergent AEs (TEAE) were AEs that began while the subject was taking study treatment or up to 2 days after the end of study treatment. TEAEs with regard to heart rate and blood pressure included tachycardia/sinus tachycardia, hypotension, and syncope.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From initiation of study treatment until 12 weeks

Notes:

[3] - 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: Descriptive statistics were done and inferential statistics were not planned as this is an open, single-group study.

|                               |   |  |  |  |
|-------------------------------|---|--|--|--|
| <b>End point values</b>       | Riociguat<br>(Adempas,<br>BAY63-2521)<br>Main Study |  |  |  |
| Subject group type            | Reporting group                                     |  |  |  |
| Number of subjects analysed   | 75 <sup>[4]</sup>                                   |  |  |  |
| Units: Subjects               |   |  |  |  |
| Tachycardia/sinus tachycardia | 11  |  |  |  |
| Hypotension                   | 11  |  |  |  |
| Syncope                       | 4   |  |  |  |

Notes:

[4] - Safety set (main study).

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Subjects Categorized According to Their Absolute QTc Values (Bazett and Fridericia) at Specified Time Points in the Main Study

|                 |   |
|-----------------|---|
| End point title | Number of Subjects Categorized According to Their Absolute QTc Values (Bazett and Fridericia) at Specified Time Points in the Main Study <sup>[5]</sup> |
|-----------------|---|

End point description:

Subjects were categorized (less than or equal to [ $\leq$ ] 450, greater than [ $>$ ] 450 to 500 and  $>500$  milliseconds [msec]) and distributed according to their absolute QTc values, calculated by Bazett and Fridericia formulae.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-study and Days 0, 1, 14, 28, 42, 56, 70, 84, and 85

Notes:

[5] - 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: Descriptive statistics were done and inferential statistics were not planned as this is an open, single-group study.



| End point values                       | Riociguat<br>(Adempas,<br>BAY63-2521)<br>Main Study |  |  |  |
|--|---|--|--|--|
| Subject group type                     | Reporting group                                     |  |  |  |
| Number of subjects analysed            | 40 <sup>[6]</sup>                                   |  |  |  |
| Units: Subjects                        |   |  |  |  |
| Bazett: ≤450 msec at pre-study         | 36  |  |  |  |
| Bazett: >450-500 msec at pre-study     | 1   |  |  |  |
| Bazett: >500 msec at pre-study         | 0   |  |  |  |
| Bazett: ≤450 msec on Day 0             | 36  |  |  |  |
| Bazett: >450-500 msec on Day 0         | 3   |  |  |  |
| Bazett: >500 msec on Day 0             | 0   |  |  |  |
| Bazett: ≤450 msec on Day 1             | 29  |  |  |  |
| Bazett: >450-500 msec on Day 1         | 6   |  |  |  |
| Bazett: >500 msec on Day 1             | 0   |  |  |  |
| Bazett: ≤450 msec on Day 14            | 34  |  |  |  |
| Bazett: >450-500 msec on Day 14        | 5   |  |  |  |
| Bazett: >500 msec on Day 14            | 0   |  |  |  |
| Bazett: ≤450 msec on Day 28            | 35  |  |  |  |
| Bazett: >450-500 msec on Day 28        | 4   |  |  |  |
| Bazett: >500 msec on Day 28            | 0   |  |  |  |
| Bazett: ≤450 msec on Day 42            | 31  |  |  |  |
| Bazett: >450-500 msec on Day 42        | 6   |  |  |  |
| Bazett: >500 msec on Day 42            | 0   |  |  |  |
| Bazett: ≤450 msec on Day 56            | 34  |  |  |  |
| Bazett: >450-500 msec on Day 56        | 3   |  |  |  |
| Bazett: >500 msec on Day 56            | 0   |  |  |  |
| Bazett: ≤450 msec on Day 70            | 34  |  |  |  |
| Bazett: >450-500 msec on Day 70        | 4   |  |  |  |
| Bazett: >500 msec on Day 70            | 0   |  |  |  |
| Bazett: ≤450 msec on Day 84            | 31  |  |  |  |
| Bazett: >450-500 msec on Day 84        | 5   |  |  |  |
| Bazett: >500 msec on Day 84            | 0   |  |  |  |
| Bazett: ≤450 msec on Day 85            | 13  |  |  |  |
| Bazett: >450-500 msec on Day 85        | 0   |  |  |  |
| Bazett: >500 msec on Day 85            | 0   |  |  |  |
| Fridericia: ≤450 msec at pre-study     | 37  |  |  |  |
| Fridericia: >450-500 msec at pre-study | 0   |  |  |  |
| Fridericia: >500 msec at pre-study     | 0   |  |  |  |
| Fridericia: ≤450 msec on Day 0         | 39  |  |  |  |
| Fridericia: >450-500 msec on Day 0     | 0   |  |  |  |
| Fridericia: >500 msec on Day 0         | 0   |  |  |  |
| Fridericia: ≤450 msec on Day 1         | 35  |  |  |  |
| Fridericia: >450-500 msec on Day 1     | 0   |  |  |  |
| Fridericia: >500 msec on Day 1         | 0   |  |  |  |
| Fridericia: ≤450 msec on Day 14        | 38  |  |  |  |
| Fridericia: >450-500 msec on Day 14    | 1   |  |  |  |
| Fridericia: >500 msec on Day 14        | 0   |  |  |  |
| Fridericia: ≤450 msec on Day 28        | 37  |  |  |  |
| Fridericia: >450-500 msec on Day 28    | 2   |  |  |  |
| Fridericia: >500 msec on Day 28        | 0   |  |  |  |
| Fridericia: ≤450 msec on Day 42        | 37  |  |  |  |

|                                     |    |  |  |  |
|-------------------------------------|----|--|--|--|
| Fridericia: >450-500 msec on Day 42 | 0  |  |  |  |
| Fridericia: >500 msec on Day 42     | 0  |  |  |  |
| Fridericia: <=450 msec on Day 56    | 37 |  |  |  |
| Fridericia: >450-500 msec on Day 56 | 0  |  |  |  |
| Fridericia: >500 msec on Day 56     | 0  |  |  |  |
| Fridericia: <=450 msec on Day 70    | 37 |  |  |  |
| Fridericia: >450-500 msec on Day 70 | 1  |  |  |  |
| Fridericia: >500 msec on Day 70     | 0  |  |  |  |
| Fridericia: <=450 msec on Day 84    | 34 |  |  |  |
| Fridericia: >450-500 msec on Day 84 | 2  |  |  |  |
| Fridericia: >500 msec on Day 84     | 0  |  |  |  |
| Fridericia: <=450 msec on Day 85    | 13 |  |  |  |
| Fridericia: >450-500 msec on Day 85 | 0  |  |  |  |
| Fridericia: >500 msec on Day 85     | 0  |  |  |  |

Notes:

[6] - Safety set (main study) with electrocardiogram valid for QT/QTc evaluation at all time points.

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With Treatment-emergent Adverse Events Leading to Discontinuation of Study Drug in the Main Study and the Long-term Extension Phase

|                 |   |
|-----------------|---|
| End point title | Number of Subjects With Treatment-emergent Adverse Events Leading to Discontinuation of Study Drug in the Main Study and the Long-term Extension Phase <sup>[7]</sup> |
|-----------------|---|

End point description:

An AE is any untoward medical occurrence (that is, any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. TEAEs were AEs that began while the subject was taking study treatment or up to 2 days after the end of study treatment. Here n = number of subjects evaluable at the specific period.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From the start of main study (12 weeks) until the end of LTE phase (84 months)

Notes:

[7] - 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: Descriptive statistics were done and inferential statistics were not planned as this is an open, single-group study.

|                             |   |  |  |  |
|-----------------------------|---|--|--|--|
| <b>End point values</b>     | Riociguat<br>(Adempas,<br>BAY63-2521)<br>Main Study |  |  |  |
| Subject group type          | Reporting group                                     |  |  |  |
| Number of subjects analysed | 75  |  |  |  |
| Units: Subjects             |   |  |  |  |
| Main Study (n = 75)         | 0   |  |  |  |
| LTE Phase (n = 68)          | 13  |  |  |  |

## Statistical analyses

## Secondary: Change From Baseline in 6-minute Walk Time Distance (6MWD) at Specified Time Points

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in 6-minute Walk Time Distance (6MWD) at Specified Time Points |
|-----------------|---|

### End point description:

6MWD is a measure for the objective evaluation of a subject's functional exercise capacity. In the below table, 'n' signifies the number of subjects evaluable for the corresponding time points. '99999' in the table below indicates that value could not be estimated since there was only 1 subject evaluable at LTE Month 84.

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

### End point timeframe:

Baseline (pre-study defined as  $\leq 1$  week prior to start of main study), Day 84 (end of main study), LTE Months 12, 24, 36, 48, 60, 72, and 84

|                                      |   |  |  |  |
|--------------------------------------|---|--|--|--|
| <b>End point values</b>              | Riociguat<br>(Adempas,<br>BAY63-2521)<br>Main Study |  |  |  |
| Subject group type                   | Reporting group                                     |  |  |  |
| Number of subjects analysed          | 68 <sup>[8]</sup>                                   |  |  |  |
| Units: Meters                        |   |  |  |  |
| arithmetic mean (standard deviation) |   |  |  |  |
| Baseline (n=68)                      | 364.9 ( $\pm$ 103.3)                                |  |  |  |
| Change at Day 84 (n=66)              | 66.3 ( $\pm$ 71)                                    |  |  |  |
| Change at LTE Month 12 (n=52)        | 58.3 ( $\pm$ 78.8)                                  |  |  |  |
| Change at LTE Month 24 (n=48)        | 72.7 ( $\pm$ 94.4)                                  |  |  |  |
| Change at LTE Month 36 (n=49)        | 64.2 ( $\pm$ 93.3)                                  |  |  |  |
| Change at LTE Month 48 (n=42)        | 69.1 ( $\pm$ 104.5)                                 |  |  |  |
| Change at LTE Month 60 (n=40)        | 55.1 ( $\pm$ 102.2)                                 |  |  |  |
| Change at LTE Month 72 (n=36)        | 57.8 ( $\pm$ 103.6)                                 |  |  |  |
| Change at LTE Month 84 (n=1)         | 297 ( $\pm$ 99999)                                  |  |  |  |

### Notes:

[8] - All subjects who entered the LTE phase.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With World Health Organization (WHO) Functional Class Assessment at Specified Time Points

|                 |  |
|-----------------|--|
| End point title | Number of Subjects With World Health Organization (WHO) Functional Class Assessment at Specified Time Points |
|-----------------|--|

### End point description:

The WHO functional assessment of pulmonary arterial hypertension ranged from functional class I (subjects with pulmonary hypertension but without resulting limitation of physical activity) to class IV (subjects with pulmonary hypertension with inability to carry out any physical activity without symptoms. These subjects manifest signs of right-heart failure). In the below table, 'n' signifies the number of subjects evaluable for the corresponding time points.

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

End point timeframe:

Pre-study (<=1 week prior to start of study), Day 84 (end of main study), LTE Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78, 81, and 84

| End point values                                 | Riociguat<br>(Adempas,<br>BAY63-2521)<br>Main Study |  |  |  |
|--|---|--|--|--|
| Subject group type                               | Reporting group                                     |  |  |  |
| Number of subjects analysed                      | 68 <sup>[9]</sup>                                   |  |  |  |
| Units: Subjects                                  |   |  |  |  |
| Pre-study: WHO Functional Class I<br>(n=68)      | 0   |  |  |  |
| Pre-study: WHO Functional Class II<br>(n=68)     | 14  |  |  |  |
| Pre-study: WHO Functional Class III<br>(n=68)    | 53  |  |  |  |
| Pre-study: WHO Functional Class IV<br>(n=68)     | 1   |  |  |  |
| Day 84: WHO Functional Class I (n=68)            | 2   |  |  |  |
| Day 84: WHO Functional Class II (n=68)           | 30  |  |  |  |
| Day 84: WHO Functional Class III<br>(n=68)       | 36  |  |  |  |
| Day 84: WHO Functional Class IV<br>(n=68)        | 0   |  |  |  |
| LTE Month 3: WHO Functional Class I<br>(n=62)    | 2   |  |  |  |
| LTE Month 3: WHO Functional Class II<br>(n=62)   | 31  |  |  |  |
| LTE Month 3: WHO Functional Class III<br>(n=62)  | 28  |  |  |  |
| LTE Month 3: WHO Functional Class IV<br>(n=62)   | 1   |  |  |  |
| LTE Month 6: WHO Functional Class I<br>(n=56)    | 2   |  |  |  |
| LTE Month 6: WHO Functional Class II<br>(n=56)   | 29  |  |  |  |
| LTE Month 6: WHO Functional Class III<br>(n=56)  | 25  |  |  |  |
| LTE Month 6: WHO Functional Class IV<br>(n=56)   | 0   |  |  |  |
| LTE Month 9: WHO Functional Class I<br>(n=52)    | 4   |  |  |  |
| LTE Month 9: WHO Functional Class II<br>(n=52)   | 27  |  |  |  |
| LTE Month 9: WHO Functional Class III<br>(n=52)  | 21  |  |  |  |
| LTE Month 9: WHO Functional Class IV<br>(n=52)   | 0   |  |  |  |
| LTE Month 12: WHO Functional Class I<br>(n=53)   | 3   |  |  |  |
| LTE Month 12: WHO Functional Class II<br>(n=53)  | 27  |  |  |  |
| LTE Month 12: WHO Functional Class III<br>(n=53) | 23  |  |  |  |
| LTE Month 12: WHO Functional Class IV<br>(n=53)  | 0   |  |  |  |

|  |    |  |  |  |
|--|----|--|--|--|
| LTE Month 15: WHO Functional Class I<br>(n=53)   | 3  |  |  |  |
| LTE Month 15: WHO Functional Class II<br>(n=53)  | 26 |  |  |  |
| LTE Month 15: WHO Functional Class III<br>(n=53) | 24 |  |  |  |
| LTE Month 15: WHO Functional Class IV<br>(n=53)  | 0  |  |  |  |
| LTE Month 18: WHO Functional Class I<br>(n=52)   | 3  |  |  |  |
| LTE Month 18: WHO Functional Class II<br>(n=52)  | 25 |  |  |  |
| LTE Month 18: WHO Functional Class III<br>(n=52) | 24 |  |  |  |
| LTE Month 18: WHO Functional Class IV<br>(n=52)  | 0  |  |  |  |
| LTE Month 21: WHO Functional Class I<br>(n=51)   | 3  |  |  |  |
| LTE Month 21: WHO Functional Class II<br>(n=51)  | 28 |  |  |  |
| LTE Month 21: WHO Functional Class III<br>(n=51) | 18 |  |  |  |
| LTE Month 21: WHO Functional Class IV<br>(n=51)  | 2  |  |  |  |
| LTE Month 24: WHO Functional Class I<br>(n=49)   | 3  |  |  |  |
| LTE Month 24: WHO Functional Class II<br>(n=49)  | 29 |  |  |  |
| LTE Month 24: WHO Functional Class III<br>(n=49) | 17 |  |  |  |
| LTE Month 24: WHO Functional Class IV<br>(n=49)  | 0  |  |  |  |
| LTE Month 27: WHO Functional Class I<br>(n=51)   | 3  |  |  |  |
| LTE Month 27: WHO Functional Class II<br>(n=51)  | 29 |  |  |  |
| LTE Month 27: WHO Functional Class III<br>(n=51) | 19 |  |  |  |
| LTE Month 27: WHO Functional Class IV<br>(n=51)  | 0  |  |  |  |
| LTE Month 30: WHO Functional Class I<br>(n=51)   | 2  |  |  |  |
| LTE Month 30: WHO Functional Class II<br>(n=51)  | 29 |  |  |  |
| LTE Month 30: WHO Functional Class III<br>(n=51) | 20 |  |  |  |
| LTE Month 30: WHO Functional Class IV<br>(n=51)  | 0  |  |  |  |
| LTE Month 33: WHO Functional Class I<br>(n=50)   | 2  |  |  |  |
| LTE Month 33: WHO Functional Class II<br>(n=50)  | 31 |  |  |  |
| LTE Month 33: WHO Functional Class III<br>(n=50) | 17 |  |  |  |
| LTE Month 33: WHO Functional Class IV<br>(n=50)  | 0  |  |  |  |
| LTE Month 36: WHO Functional Class I<br>(n=50)   | 3  |  |  |  |
| LTE Month 36: WHO Functional Class II<br>(n=50)  | 30 |  |  |  |
| LTE Month 36: WHO Functional Class III<br>(n=50) | 17 |  |  |  |

|  |    |  |  |  |
|--|----|--|--|--|
| LTE Month 36: WHO Functional Class IV<br>(n=50)  | 0  |  |  |  |
| LTE Month 39: WHO Functional Class I<br>(n=50)   | 3  |  |  |  |
| LTE Month 39: WHO Functional Class II<br>(n=50)  | 25 |  |  |  |
| LTE Month 39: WHO Functional Class III<br>(n=50) | 22 |  |  |  |
| LTE Month 39: WHO Functional Class IV<br>(n=50)  | 0  |  |  |  |
| LTE Month 42: WHO Functional Class I<br>(n=48)   | 3  |  |  |  |
| LTE Month 42: WHO Functional Class II<br>(n=48)  | 23 |  |  |  |
| LTE Month 42: WHO Functional Class III<br>(n=48) | 22 |  |  |  |
| LTE Month 42: WHO Functional Class IV<br>(n=48)  | 0  |  |  |  |
| LTE Month 45: WHO Functional Class I<br>(n=47)   | 3  |  |  |  |
| LTE Month 45: WHO Functional Class II<br>(n=47)  | 25 |  |  |  |
| LTE Month 45: WHO Functional Class III<br>(n=47) | 18 |  |  |  |
| LTE Month 45: WHO Functional Class IV<br>(n=47)  | 1  |  |  |  |
| LTE Month 48: WHO Functional Class I<br>(n=44)   | 3  |  |  |  |
| LTE Month 48: WHO Functional Class II<br>(n=44)  | 25 |  |  |  |
| LTE Month 48: WHO Functional Class III<br>(n=44) | 16 |  |  |  |
| LTE Month 48: WHO Functional Class IV<br>(n=44)  | 0  |  |  |  |
| LTE Month 51: WHO Functional Class I<br>(n=44)   | 3  |  |  |  |
| LTE Month 51: WHO Functional Class II<br>(n=44)  | 27 |  |  |  |
| LTE Month 51: WHO Functional Class III<br>(n=44) | 14 |  |  |  |
| LTE Month 51: WHO Functional Class IV<br>(n=44)  | 0  |  |  |  |
| LTE Month 54: WHO Functional Class I<br>(n=42)   | 4  |  |  |  |
| LTE Month 54: WHO Functional Class II<br>(n=42)  | 25 |  |  |  |
| LTE Month 54: WHO Functional Class III<br>(n=42) | 13 |  |  |  |
| LTE Month 54: WHO Functional Class IV<br>(n=42)  | 0  |  |  |  |
| LTE Month 57: WHO Functional Class I<br>(n=42)   | 4  |  |  |  |
| LTE Month 57: WHO Functional Class II<br>(n=42)  | 23 |  |  |  |
| LTE Month 57: WHO Functional Class III<br>(n=42) | 14 |  |  |  |
| LTE Month 57: WHO Functional Class IV<br>(n=42)  | 1  |  |  |  |
| LTE Month 60: WHO Functional Class I<br>(n=41)   | 3  |  |  |  |
| LTE Month 60: WHO Functional Class II<br>(n=41)  | 23 |  |  |  |

|  |    |  |  |  |
|--|----|--|--|--|
| LTE Month 60: WHO Functional Class III<br>(n=41) | 15 |  |  |  |
| LTE Month 60: WHO Functional Class IV<br>(n=41)  | 0  |  |  |  |
| LTE Month 63: WHO Functional Class I<br>(n=41)   | 3  |  |  |  |
| LTE Month 63: WHO Functional Class II<br>(n=41)  | 22 |  |  |  |
| LTE Month 63: WHO Functional Class III<br>(n=41) | 15 |  |  |  |
| LTE Month 63: WHO Functional Class IV<br>(n=41)  | 1  |  |  |  |
| LTE Month 66: WHO Functional Class I<br>(n=39)   | 4  |  |  |  |
| LTE Month 66: WHO Functional Class II<br>(n=39)  | 21 |  |  |  |
| LTE Month 66: WHO Functional Class III<br>(n=39) | 14 |  |  |  |
| LTE Month 66: WHO Functional Class IV<br>(n=39)  | 0  |  |  |  |
| LTE Month 69: WHO Functional Class I<br>(n=38)   | 3  |  |  |  |
| LTE Month 69: WHO Functional Class II<br>(n=38)  | 23 |  |  |  |
| LTE Month 69: WHO Functional Class III<br>(n=38) | 12 |  |  |  |
| LTE Month 69: WHO Functional Class IV<br>(n=38)  | 0  |  |  |  |
| LTE Month 72: WHO Functional Class I<br>(n=37)   | 3  |  |  |  |
| LTE Month 72: WHO Functional Class II<br>(n=37)  | 21 |  |  |  |
| LTE Month 72: WHO Functional Class III<br>(n=37) | 13 |  |  |  |
| LTE Month 72: WHO Functional Class IV<br>(n=37)  | 0  |  |  |  |
| LTE Month 75: WHO Functional Class I<br>(n=33)   | 4  |  |  |  |
| LTE Month 75: WHO Functional Class II<br>(n=33)  | 18 |  |  |  |
| LTE Month 75: WHO Functional Class III<br>(n=33) | 11 |  |  |  |
| LTE Month 75: WHO Functional Class IV<br>(n=33)  | 0  |  |  |  |
| LTE Month 78: WHO Functional Class I<br>(n=19)   | 1  |  |  |  |
| LTE Month 78: WHO Functional Class II<br>(n=19)  | 7  |  |  |  |
| LTE Month 78: WHO Functional Class III<br>(n=19) | 11 |  |  |  |
| LTE Month 78: WHO Functional Class IV<br>(n=19)  | 0  |  |  |  |
| LTE Month 81: WHO Functional Class I<br>(n=10)   | 1  |  |  |  |
| LTE Month 81: WHO Functional Class II<br>(n=10)  | 4  |  |  |  |
| LTE Month 81: WHO Functional Class III<br>(n=10) | 5  |  |  |  |
| LTE Month 81: WHO Functional Class IV<br>(n=10)  | 0  |  |  |  |
| LTE Month 84: WHO Functional Class I<br>(n=2)    | 1  |  |  |  |

|  |   |  |  |  |
|--|---|--|--|--|
| LTE Month 84: WHO Functional Class II (n=2)  | 0 |  |  |  |
| LTE Month 84: WHO Functional Class III (n=2) | 1 |  |  |  |
| LTE Month 84: WHO Functional Class IV (n=2)  | 0 |  |  |  |

Notes:

[9] - All subjects who entered the LTE phase.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Echocardiographic Results - Tei Index at Day 84 in the Main Study

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Echocardiographic Results - Tei Index at Day 84 in the Main Study |
|-----------------|---|

End point description:

Tei index = myocardial performance index (isovolumic contraction time plus isovolumic relaxation time divided by right ventricular ejection time). In the below table, 'n' signifies the number of subjects evaluable for the corresponding time points. Please find the statistical analyses in the attachment below.

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

End point timeframe:

Baseline (pre-study defined as  $\leq 1$  week prior to start of study) and Day 84

|                                      |  |  |  |  |
|--------------------------------------|--|--|--|--|
| <b>End point values</b>              | Riociguat (Adempas, BAY63-2521) Main Study |  |  |  |
| Subject group type                   | Reporting group                            |  |  |  |
| Number of subjects analysed          | 72 <sup>[10]</sup>                         |  |  |  |
| Units: Ratio                         |  |  |  |  |
| arithmetic mean (standard deviation) |  |  |  |  |
| Baseline (n=46)                      | 0.708 ( $\pm$ 0.341)                       |  |  |  |
| Change at Day 84 (n=35)              | -0.176 ( $\pm$ 0.28)                       |  |  |  |

Notes:

[10] - PK/PD set (main study).

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Echocardiographic Results - Pulmonary Arterial Systolic Pressure (PASP) at Day 84 in the Main Study

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Echocardiographic Results - Pulmonary Arterial Systolic Pressure (PASP) at Day 84 in the Main Study |
|-----------------|---|

End point description:

PASP is composed of the right ventricular systolic pressure as measured over the tricuspid regurgitation jet (4xtricuspid regurgitation jet peak velocity) plus the systolic venous pressure according to width of the vena cava inferior measured in M-mode. In the below table, 'n' signifies the number of subjects



evaluable for the corresponding time points. Please find the statistical analyses in the attachment below.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Baseline (pre-study defined as $\leq 1$ week prior to start of study) and Day 84 |           |

|                                      |   |  |  |  |
|--------------------------------------|---|--|--|--|
| <b>End point values</b>              | Riociguat<br>(Adempas,<br>BAY63-2521)<br>Main Study |  |  |  |
| Subject group type                   | Reporting group                                     |  |  |  |
| Number of subjects analysed          | 72 <sup>[11]</sup>                                  |  |  |  |
| Units: millimeter of mercury (mmHg)  |   |  |  |  |
| arithmetic mean (standard deviation) |   |  |  |  |
| Baseline (n=65)                      | 73.6 ( $\pm$ 20.6)                                  |  |  |  |
| Change at Day 84 (n=58)              | -6.9 ( $\pm$ 16.7)                                  |  |  |  |

Notes:

[11] - PK/PD set (main study).

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Echocardiographic Results - Tricuspid Annular Plane Systolic Excursion (TAPSE) at Day 84 in the Main Study

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Echocardiographic Results - Tricuspid Annular Plane Systolic Excursion (TAPSE) at Day 84 in the Main Study |
|-----------------|--|

End point description:

In a modified apical 4-chamber view, the excursions of the tricuspid annular plane were measured by positioning the M-mode cursor on the lateral portion of the tricuspid annulus; this movement reflected the base to apex shortening of the right ventricle in systole; movement  $>2$  centimeters (cm) indicates good contraction, 12 cm indicate poor contraction, and less than ( $<$ ) 1 cm indicates heart failure. In the below table, 'n' signifies the number of subjects evaluable for the corresponding time points. Please find the statistical analyses in the attachment below.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Baseline (pre-study defined as $\leq 1$ week prior to start of study) and Day 84 |           |

|                                      |   |  |  |  |
|--------------------------------------|---|--|--|--|
| <b>End point values</b>              | Riociguat<br>(Adempas,<br>BAY63-2521)<br>Main Study |  |  |  |
| Subject group type                   | Reporting group                                     |  |  |  |
| Number of subjects analysed          | 72 <sup>[12]</sup>                                  |  |  |  |
| Units: centimeters                   |   |  |  |  |
| arithmetic mean (standard deviation) |   |  |  |  |
| Baseline (n=64)                      | 1.741 ( $\pm$ 0.586)                                |  |  |  |
| Change at Day 84 (n=59)              | 0.276 ( $\pm$ 0.491)                                |  |  |  |

Notes:

[12] - PK/PD set (main study).

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Swan-Ganz Hemodynamic Parameters - Blood/Artery/Atrial/Capillary Pressure at Day 84 in the Main Study

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Swan-Ganz Hemodynamic Parameters - Blood/Artery/Atrial/Capillary Pressure at Day 84 in the Main Study |
|-----------------|---|

End point description:

The following Swan-Ganz hemodynamic parameters related to blood/artery/atrial/capillary pressure during right heart catheterization were measured: mean right atrial pressure (RAPmean), systolic pulmonary artery pressure (PAPsyst), diastolic pulmonary artery pressure (PAPdiast), mean pulmonary artery pressure (PAPmean), pulmonary capillary wedge pressure (PCWP), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP). In the below table, 'n' signifies the number of subjects evaluable for the respective outcomes at that time points. Please find the statistical analyses in the attachment below.

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

End point timeframe:

Baseline (pre-study defined as  $\leq 1$  week prior to start of study) and Day 84

| End point values                     | Riociguat<br>(Adempas,<br>BAY63-2521)<br>Main Study |  |  |  |
|--------------------------------------|---|--|--|--|
| Subject group type                   | Reporting group                                     |  |  |  |
| Number of subjects analysed          | 50 <sup>[13]</sup>                                  |  |  |  |
| Units: mmHg                          |   |  |  |  |
| arithmetic mean (standard deviation) |   |  |  |  |
| Baseline: RAPmean (n=50)             | 6.6 (± 4.3)   |  |  |  |
| Change at Day 84: RAPmean (n=50)     | 0.3 (± 5.2)   |  |  |  |
| Baseline: PAPsyst (n=50)             | 77.5 (± 15.1)                                       |  |  |  |
| Change at Day 84: PAPsyst (n=48)     | -7.3 (± 14.1)                                       |  |  |  |
| Baseline: PAPdiast (n=50)            | 27.5 (± 10.9)                                       |  |  |  |
| Change at Day 84: PAPdiast (n=48)    | -4.8 (± 9.2)  |  |  |  |
| Baseline: PAPmean (n=50)             | 45.3 (± 10.8)                                       |  |  |  |
| Change at Day 84: PAPmean (n=50)     | -5.3 (± 8.6)  |  |  |  |
| Baseline: PCWP (n=50)                | 8 (± 4.2)   |  |  |  |
| Change at Day 84: PCWP (n=50)        | 1.2 (± 4.4)   |  |  |  |
| Baseline: SBP (n=47)                 | 129.3 (± 19.3)                                      |  |  |  |
| Change at Day 84: SBP (n=47)         | -7.5 (± 18.2)                                       |  |  |  |
| Baseline: DBP (n=47)                 | 78.4 (± 12.8)                                       |  |  |  |
| Change at Day 84: DBP (n=47)         | -7.2 (± 14.2)                                       |  |  |  |
| Baseline: MAP (n=45)                 | 95.5 (± 16.6)                                       |  |  |  |
| Change at Day 84: MAP (n=45)         | -5.3 (± 17.7)                                       |  |  |  |

Notes:

[13] - PK/PD population (main study) with available measurements for this endpoint.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Swan-Ganz Hemodynamic Parameters - Heart Rate at Day 84 in the Main Study

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Swan-Ganz Hemodynamic Parameters - Heart Rate at Day 84 in the Main Study |
|-----------------|---|

End point description:

Heart rate was measured during right heart catheterization. In the below table, 'n' signifies the number of subjects evaluable at the corresponding time points.

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

End point timeframe:

Baseline (pre-study defined as  $\leq 1$  week prior to start of study) and Day 84

|                                      |   |  |  |  |
|--------------------------------------|---|--|--|--|
| <b>End point values</b>              | Riociguat<br>(Adempas,<br>BAY63-2521)<br>Main Study |  |  |  |
| Subject group type                   | Reporting group                                     |  |  |  |
| Number of subjects analysed          | 50 <sup>[14]</sup>                                  |  |  |  |
| Units: beats per minute              |   |  |  |  |
| arithmetic mean (standard deviation) |   |  |  |  |
| Baseline (n=49)                      | 77 ( $\pm$ 12.1)                                    |  |  |  |
| Change at Day 84 (n=50)              | 0.9 ( $\pm$ 11.8)                                   |  |  |  |

Notes:

[14] - PK/PD population (main study) with available measurements for this endpoint.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Swan-Ganz Hemodynamic Parameters - Vascular Resistance at Day 84 in the Main Study

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Swan-Ganz Hemodynamic Parameters - Vascular Resistance at Day 84 in the Main Study |
|-----------------|--|

End point description:

Systemic and pulmonary vascular resistance parameters were calculated as follows: Systemic vascular resistance (SVR)= $80 \times (\text{MAP} - \text{RAP}_{\text{mean}}) / \text{cardiac output}$ , and pulmonary vascular resistance (PVR)= $80 \times (\text{PAP}_{\text{mean}} - \text{PCWP}) / \text{cardiac output}$ . SVR and PVR were expressed in  $\text{dyne} \times \text{second} \times \text{centimeter}^{-5}$ . 1  $\text{dyne} = 1 \text{ gram} \times \text{centimeter} \times \text{second}^{-2} = 10^{-5}$  Newton. In the below table, 'n' signifies the number of subjects evaluable for the respective outcomes at that time points. Please find the statistical analyses in the attachment below.

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

End point timeframe:

Baseline (pre-study defined as  $\leq 1$  week prior to start of study) and Day 84

|  |   |  |  |  |
|--|---|--|--|--|
| <b>End point values</b>                    | Riociguat<br>(Adempas,<br>BAY63-2521)<br>Main Study |  |  |  |
| Subject group type                         | Reporting group                                     |  |  |  |
| Number of subjects analysed                | 50 <sup>[15]</sup>                                  |  |  |  |
| Units: dyne*second*centimeter <sup>5</sup> |   |  |  |  |
| arithmetic mean (standard deviation)       |   |  |  |  |
| Baseline: SVR (n=45)                       | 1815 ( $\pm$ 638)                                   |  |  |  |
| Change at Day 84: SVR (n=44)               | -399 ( $\pm$ 589)                                   |  |  |  |
| Baseline: PVR (n=50)                       | 778 ( $\pm$ 351)                                    |  |  |  |
| Change at Day 84: PVR (n=48)               | -253 ( $\pm$ 209)                                   |  |  |  |

Notes:

[15] - PK/PD population (main study) with available measurements for this endpoint.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Swan-Ganz Hemodynamic Parameters - Percentage Vascular Resistance Ratio at Day 84 in the Main Study

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Swan-Ganz Hemodynamic Parameters - Percentage Vascular Resistance Ratio at Day 84 in the Main Study |
|-----------------|---|

End point description:

Ratio of PVR/SVR was reported in terms of percentage.  $SVR = 80 * (MAP - RAP_{mean}) / \text{cardiac output}$ , and  $PVR = 80 * (PAP_{mean} - PCWP) / \text{cardiac output}$ . In the below table, 'n' signifies the number of subjects evaluable at the corresponding time points. Please find the statistical analyses in the attachment below.

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

End point timeframe:

Baseline (pre-study defined as  $\leq 1$  week prior to start of study) and Day 84

|                                      |   |  |  |  |
|--------------------------------------|---|--|--|--|
| <b>End point values</b>              | Riociguat<br>(Adempas,<br>BAY63-2521)<br>Main Study |  |  |  |
| Subject group type                   | Reporting group                                     |  |  |  |
| Number of subjects analysed          | 50 <sup>[16]</sup>                                  |  |  |  |
| Units: Percentage of Ratio           |   |  |  |  |
| arithmetic mean (standard deviation) |   |  |  |  |
| Baseline (n=45)                      | 45.2 ( $\pm$ 15.8)                                  |  |  |  |
| Change at Day 84 (n=44)              | -6.2 ( $\pm$ 14.5)                                  |  |  |  |

Notes:

[16] - PK/PD population (main study) with available measurements for this endpoint.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Swan-Ganz Hemodynamic Parameters - Vascular Resistance Index at Day 84 in the Main Study

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Swan-Ganz Hemodynamic Parameters - Vascular Resistance Index at Day 84 in the Main Study |
|-----------------|--|

End point description:

Systemic and pulmonary vascular resistance indices were calculated as follows: SVR index (SVRI)=80\*(MAP-RAPmean)/cardiac output\*body surface area, and PVR index (PVRI)=80\*(PAPmean PCWP)/cardiac output\*body surface area. SVRI and PVRI were expressed in dyne\*second\*centimeter<sup>5</sup>\*square meter. 1 dyne=1 gram\*centimeter\*second<sup>2</sup>= 10<sup>5</sup> Newton. In the below table, 'n' signifies the number of subjects evaluable for the respective outcomes at that time points. Please find the statistical analyses in the attachment below.

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

End point timeframe:

Baseline (pre-study defined as ≤1 week prior to start of study) and Day 84

|  |   |  |  |  |
|--|---|--|--|--|
| <b>End point values</b>                                  | Riociguat<br>(Adempas,<br>BAY63-2521)<br>Main Study |  |  |  |
| Subject group type                                       | Reporting group                                     |  |  |  |
| Number of subjects analysed                              | 50 <sup>[17]</sup>                                  |  |  |  |
| Units: dyne*second*centimeter <sup>5</sup> *square meter |   |  |  |  |
| arithmetic mean (standard deviation)                     |   |  |  |  |
| Baseline: SVRI (n=45)                                    | 3380 (± 1081)                                       |  |  |  |
| Change at Day 84: SVRI (n=44)                            | -736 (± 1125)                                       |  |  |  |
| Baseline: PVRI (n=50)                                    | 1436 (± 615)  |  |  |  |
| Change at Day 84: PVRI (n=48)                            | -466 (± 385)  |  |  |  |

Notes:

[17] - PK/PD population (main study) with available measurements for this endpoint.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Swan-Ganz Hemodynamic Parameters - Cardiac Output at Day 84 in the Main Study

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Swan-Ganz Hemodynamic Parameters - Cardiac Output at Day 84 in the Main Study |
|-----------------|---|

End point description:

Cardiac output was measured in triplicate, performed and calculated by cardiac output device. In the below table, 'n' signifies the number of subjects evaluable at the corresponding time points. Please find the statistical analyses in the attachment below.

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

End point timeframe:

Baseline (pre-study defined as ≤1 week prior to start of study) and Day 84

|                                      |   |  |  |  |
|--------------------------------------|---|--|--|--|
| <b>End point values</b>              | Riociguat<br>(Adempas,<br>BAY63-2521)<br>Main Study |  |  |  |
| Subject group type                   | Reporting group                                     |  |  |  |
| Number of subjects analysed          | 50 <sup>[18]</sup>                                  |  |  |  |
| Units: liter per minute              |   |  |  |  |
| arithmetic mean (standard deviation) |   |  |  |  |
| Baseline (n=50)                      | 4.2 (± 1.2)   |  |  |  |
| Change at Day 84 (n=48)              | 0.88 (± 0.98)                                       |  |  |  |

Notes:

[18] - PK/PD population (main study) with available measurements for this endpoint.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Swan-Ganz Hemodynamic Parameters - Cardiac Index at Day 84 in the Main Study

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Swan-Ganz Hemodynamic Parameters - Cardiac Index at Day 84 in the Main Study |
|-----------------|--|

End point description:

Cardiac index = cardiac output / body surface area. In the below table, 'n' signifies the number of subjects evaluable at the corresponding time points. Please find the statistical analyses in the attachment below.

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

End point timeframe:

Baseline (pre-study defined as ≤1 week prior to start of study) and Day 84

|  |   |  |  |  |
|--|---|--|--|--|
| <b>End point values</b>                  | Riociguat<br>(Adempas,<br>BAY63-2521)<br>Main Study |  |  |  |
| Subject group type                       | Reporting group                                     |  |  |  |
| Number of subjects analysed              | 50 <sup>[19]</sup>                                  |  |  |  |
| Units: liter per minute per square meter |   |  |  |  |
| arithmetic mean (standard deviation)     |   |  |  |  |
| Baseline (n=50)                          | 2.24 (± 0.59)                                       |  |  |  |
| Change at Day 84 (n=48)                  | 0.48 (± 0.51)                                       |  |  |  |

Notes:

[19] - PK/PD population (main study) with available measurements for this endpoint.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in N-terminal Pro-hormone B-type Natriuretic

## Peptide (NT-proBNP) Levels at Specified Time Points

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in N-terminal Pro-hormone B-type Natriuretic Peptide (NT-proBNP) Levels at Specified Time Points |
|-----------------|---|

End point description:

In the below table, 'n' signifies the number of subjects evaluable for the respective outcomes at that time points.

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

End point timeframe:

Baseline (pre-study defined as  $\leq 1$  week prior to start of main study), Day 84 (end of main study), LTE Months 12, 24, 36, 48, 60, and 69

|                                      |   |  |  |  |
|--------------------------------------|---|--|--|--|
| <b>End point values</b>              | Riociguat<br>(Adempas,<br>BAY63-2521)<br>Main Study |  |  |  |
| Subject group type                   | Reporting group                                     |  |  |  |
| Number of subjects analysed          | 72 <sup>[20]</sup>                                  |  |  |  |
| Units: picogram per milliliter       |   |  |  |  |
| arithmetic mean (standard deviation) |   |  |  |  |
| Baseline (n=53)                      | 9081 ( $\pm$ 5204)                                  |  |  |  |
| Change at Day 84 (n=51)              | -1736 ( $\pm$ 2952)                                 |  |  |  |
| Change at LTE Month 12 (n=36)        | -1334 ( $\pm$ 4138)                                 |  |  |  |
| Change at LTE Month 24 (n=37)        | -214 ( $\pm$ 3342)                                  |  |  |  |
| Change at LTE Month 36 (n=37)        | 305 ( $\pm$ 5305)                                   |  |  |  |
| Change at LTE Month 48 (n=34)        | 2169 ( $\pm$ 8072)                                  |  |  |  |
| Change at LTE Month 60 (n=24)        | 2636 ( $\pm$ 7277)                                  |  |  |  |
| Change at LTE Month 69 (n=0)         | 99999 ( $\pm$ 99999)                                |  |  |  |

Notes:

[20] - PK/PD set (main study).

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From time of an AE that began while the subject was taking study treatment or up to 2 days after the end of study treatment

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

### Reporting groups

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Riociguat (Adempas, BAY63-2521) |
|-----------------------|---------------------------------|

Reporting group description:

Subjects received Riociguat (Adempas, BAY63-2521) immediate release (IR) tablets with biweekly titrations of doses starting from 1.0 milligram (mg) thrice in a day (TID) up to 2.5 mg TID in steps of plus (+) 0.5 mg according to safety and tolerability (mainly peripheral systolic blood pressure) for 12 weeks. Subjects who were willing to continue, entered the long-term extension (LTE) phase until the premature termination of product development or until official approval and commercial availability of BAY63-2521 at a minimum dose of 0.5 mg TID and maximum dose of 2.5 mg TID.

| Serious adverse events  | Riociguat (Adempas, BAY63-2521) |  |  |
|---|---------------------------------|--|--|
| Total subjects affected by serious adverse events                   |                                 |  |  |
| subjects affected / exposed   | 54 / 68 (79.41%)                |  |  |
| number of deaths (all causes)                                       | 13                              |  |  |
| number of deaths resulting from adverse events                      |                                 |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                 |  |  |
| Breast cancer   |                                 |  |  |
| subjects affected / exposed   | 1 / 68 (1.47%)                  |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                           |  |  |
| deaths causally related to treatment / all                          | 0 / 0                           |  |  |
| Hepatocellular carcinoma  |                                 |  |  |
| subjects affected / exposed   | 1 / 68 (1.47%)                  |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                           |  |  |
| deaths causally related to treatment / all                          | 0 / 1                           |  |  |
| Uterine leiomyoma   |                                 |  |  |
| subjects affected / exposed   | 1 / 68 (1.47%)                  |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                           |  |  |
| deaths causally related to treatment / all                          | 0 / 0                           |  |  |
| Vascular disorders  |                                 |  |  |



|   |                |  |  |
|---|----------------|--|--|
| Haematoma                                       |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Thrombophlebitis                                |                |  |  |
| subjects affected / exposed                     | 2 / 68 (2.94%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Vasculitis                                      |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Surgical and medical procedures                 |                |  |  |
| Abscess drainage                                |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Angioplasty                                     |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Large intestinal polypectomy                    |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Bilevel positive airway pressure                |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Lung transplant                                 |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Mechanical ventilation                          |                |  |  |

|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                          | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Pulmonary endarterectomy                             |                |  |  |
| subjects affected / exposed                          | 2 / 68 (2.94%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Death  |                |  |  |
| subjects affected / exposed                          | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 1          |  |  |
| Chest pain   |                |  |  |
| subjects affected / exposed                          | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Oedema peripheral                                    |                |  |  |
| subjects affected / exposed                          | 2 / 68 (2.94%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Impaired healing                                     |                |  |  |
| subjects affected / exposed                          | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Hernia   |                |  |  |
| subjects affected / exposed                          | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Sudden death   |                |  |  |
| subjects affected / exposed                          | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 1          |  |  |
| Immune system disorders                              |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Hypersensitivity                                |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Reproductive system and breast disorders        |                |  |  |
| Uterine prolapse                                |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Cough   |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Chronic obstructive pulmonary disease           |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dyspnoea  |                |  |  |
| subjects affected / exposed                     | 2 / 68 (2.94%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Haemoptysis                                     |                |  |  |
| subjects affected / exposed                     | 3 / 68 (4.41%) |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pleural effusion                                |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumonia aspiration                            |                |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 68 (1.47%)   |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pulmonary haemorrhage                           |                  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%)   |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pulmonary arterial hypertension                 |                  |  |  |
| subjects affected / exposed                     | 9 / 68 (13.24%)  |  |  |
| occurrences causally related to treatment / all | 1 / 10           |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pulmonary hypertension                          |                  |  |  |
| subjects affected / exposed                     | 13 / 68 (19.12%) |  |  |
| occurrences causally related to treatment / all | 2 / 14           |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Psychiatric disorders                           |                  |  |  |
| Depression                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%)   |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Investigations                                  |                  |  |  |
| Catheterisation cardiac                         |                  |  |  |
| subjects affected / exposed                     | 2 / 68 (2.94%)   |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Blood creatine phosphokinase increased          |                  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%)   |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| International normalised ratio increased        |                  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%)   |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| Transaminases increased                         |                |  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Vascular resistance pulmonary increased         |                |  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Injury, poisoning and procedural complications  |                |  |  |  |
| Craniocerebral injury                           |                |  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Femoral neck fracture                           |                |  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |  |
| Gastrointestinal disorder postoperative         |                |  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Joint dislocation                               |                |  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Incisional hernia                               |                |  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Lumbar vertebral fracture                       |                |  |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| subjects affected / exposed                     | 2 / 68 (2.94%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Post procedural haemorrhage                     |                |  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Overdose  |                |  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Road traffic accident                           |                |  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Spinal column injury                            |                |  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Subdural haematoma                              |                |  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Subcutaneous haematoma                          |                |  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Tibia fracture                                  |                |  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Thoracic vertebral fracture                     |                |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 68 (1.47%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vascular pseudoaneurysm                         |                 |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Congenital, familial and genetic disorders      |                 |  |  |
| Hydrocele                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Atrial flutter                                  |                 |  |  |
| subjects affected / exposed                     | 6 / 68 (8.82%)  |  |  |
| occurrences causally related to treatment / all | 0 / 9           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Angina pectoris                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Chronic right ventricular failure               |                 |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiopulmonary failure                         |                 |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac failure                                 |                 |  |  |
| subjects affected / exposed                     | 8 / 68 (11.76%) |  |  |
| occurrences causally related to treatment / all | 2 / 14          |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| Right ventricular failure                       |                  |  |  |
| subjects affected / exposed                     | 13 / 68 (19.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 20           |  |  |
| deaths causally related to treatment / all      | 0 / 5            |  |  |
| Coronary artery disease                         |                  |  |  |
| subjects affected / exposed                     | 2 / 68 (2.94%)   |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cor pulmonale                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%)   |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Sick sinus syndrome                             |                  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%)   |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Supraventricular tachycardia                    |                  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%)   |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Nervous system disorders                        |                  |  |  |
| Cerebral ischaemia                              |                  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%)   |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Convulsion                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%)   |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Syncope   |                  |  |  |
| subjects affected / exposed                     | 14 / 68 (20.59%) |  |  |
| occurrences causally related to treatment / all | 6 / 36           |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Blood and lymphatic system disorders            |                  |  |  |



|   |                |  |  |
|---|----------------|--|--|
| Anaemia   |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Ear and labyrinth disorders                     |                |  |  |
| Sudden hearing loss                             |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Eye disorders                                   |                |  |  |
| Cataract  |                |  |  |
| subjects affected / exposed                     | 2 / 68 (2.94%) |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal disorders                      |                |  |  |
| Abdominal pain                                  |                |  |  |
| subjects affected / exposed                     | 2 / 68 (2.94%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Ascites   |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Constipation                                    |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Abdominal pain upper                            |                |  |  |
| subjects affected / exposed                     | 2 / 68 (2.94%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal haemorrhage                    |                |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Gastritis                                       |                |  |  |  |
| subjects affected / exposed                     | 4 / 68 (5.88%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 7          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Crohn's disease                                 |                |  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Gastrooesophageal reflux disease                |                |  |  |  |
| subjects affected / exposed                     | 2 / 68 (2.94%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 2          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Gingival bleeding                               |                |  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Intestinal haemorrhage                          |                |  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Inguinal hernia                                 |                |  |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Ileus   |                |  |  |  |
| subjects affected / exposed                     | 2 / 68 (2.94%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |  |
| Haematemesis                                    |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Umbilical hernia                                |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hepatobiliary disorders                         |                |  |  |
| Cardiac cirrhosis                               |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal and urinary disorders                     |                |  |  |
| Calculus ureteric                               |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Prerenal failure                                |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal failure                                   |                |  |  |
| subjects affected / exposed                     | 2 / 68 (2.94%) |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Osteoarthritis                                  |                |  |  |
| subjects affected / exposed                     | 2 / 68 (2.94%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Bursitis  |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                                      |  |  |  |
|---|--------------------------------------|--|--|--|
| Infections and infestations<br>Bronchopneumonia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all               | <br>1 / 68 (1.47%)<br>0 / 1<br>0 / 0 |  |  |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all  | <br>1 / 68 (1.47%)<br>0 / 1<br>0 / 0 |  |  |  |
| Gastroenteritis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | <br>2 / 68 (2.94%)<br>1 / 2<br>0 / 0 |  |  |  |
| Haematoma infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | <br>1 / 68 (1.47%)<br>0 / 1<br>0 / 0 |  |  |  |
| Infective exacerbation of chronic obstructive airways disease<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | <br>1 / 68 (1.47%)<br>0 / 1<br>0 / 0 |  |  |  |
| Osteomyelitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | <br>1 / 68 (1.47%)<br>0 / 1<br>0 / 0 |  |  |  |
| Pneumonia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | <br>5 / 68 (7.35%)<br>0 / 6<br>0 / 0 |  |  |  |
| Lymphangitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all  | <br>1 / 68 (1.47%)<br>0 / 1<br>0 / 0 |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Respiratory tract infection                     |                |  |  |
| subjects affected / exposed                     | 2 / 68 (2.94%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Sepsis  |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Septic shock                                    |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Tooth infection                                 |                |  |  |
| subjects affected / exposed                     | 1 / 68 (1.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                     | Riociguat (Adempas, BAY63-2521) |  |  |
|---|---------------------------------|--|--|
| Total subjects affected by non-serious adverse events |                                 |  |  |
| subjects affected / exposed                           | 64 / 68 (94.12%)                |  |  |
| Vascular disorders                                    |                                 |  |  |
| Haematoma   |                                 |  |  |
| subjects affected / exposed                           | 4 / 68 (5.88%)                  |  |  |
| occurrences (all)                                     | 4                               |  |  |
| Hypotension   |                                 |  |  |
| subjects affected / exposed                           | 24 / 68 (35.29%)                |  |  |
| occurrences (all)                                     | 32                              |  |  |
| General disorders and administration site conditions  |                                 |  |  |
| Chest pain  |                                 |  |  |
| subjects affected / exposed                           | 5 / 68 (7.35%)                  |  |  |
| occurrences (all)                                     | 6                               |  |  |
| Oedema  |                                 |  |  |

|  |  |  |  |
|--|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Fatigue</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oedema peripheral</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Peripheral swelling</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>19 / 68 (27.94%)</p> <p>29</p> <p>10 / 68 (14.71%)</p> <p>11</p> <p>30 / 68 (44.12%)</p> <p>59</p> <p>4 / 68 (5.88%)</p> <p>4</p>   |  |  |
| <p>Reproductive system and breast disorders</p> <p>Gynaecomastia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>4 / 68 (5.88%)</p> <p>4</p>   |  |  |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dysphonia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Epistaxis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pleural effusion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nasal congestion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pulmonary arterial hypertension</p> | <p>19 / 68 (27.94%)</p> <p>22</p> <p>10 / 68 (14.71%)</p> <p>11</p> <p>4 / 68 (5.88%)</p> <p>5</p> <p>6 / 68 (8.82%)</p> <p>12</p> <p>4 / 68 (5.88%)</p> <p>4</p> <p>4 / 68 (5.88%)</p> <p>4</p> |  |  |

|   |   |  |  |
|---|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pulmonary hypertension</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Respiratory failure</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>4 / 68 (5.88%)</p> <p>4</p> <p>13 / 68 (19.12%)</p> <p>16</p> <p>6 / 68 (8.82%)</p> <p>7</p> |  |  |
| <p>Psychiatric disorders</p> <p>Depression</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>5 / 68 (7.35%)</p> <p>5</p> <p>5 / 68 (7.35%)</p> <p>9</p>                                   |  |  |
| <p>Investigations</p> <p>International normalised ratio increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>5 / 68 (7.35%)</p> <p>5</p>  |  |  |
| <p>Injury, poisoning and procedural complications</p> <p>Contusion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Fall</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Muscle strain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>4 / 68 (5.88%)</p> <p>4</p> <p>4 / 68 (5.88%)</p> <p>4</p> <p>4 / 68 (5.88%)</p> <p>4</p>    |  |  |
| <p>Cardiac disorders</p> <p>Atrial fibrillation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Palpitations</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>6 / 68 (8.82%)</p> <p>8</p> <p>6 / 68 (8.82%)</p> <p>9</p>                                   |  |  |

|  |                        |  |  |
|--|------------------------|--|--|
| Right ventricular failure<br>subjects affected / exposed<br>occurrences (all)                          | 5 / 68 (7.35%)<br>5    |  |  |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)  | 12 / 68 (17.65%)<br>16 |  |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)              | 26 / 68 (38.24%)<br>38 |  |  |
| Head discomfort<br>subjects affected / exposed<br>occurrences (all)                                    | 4 / 68 (5.88%)<br>4    |  |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)   | 15 / 68 (22.06%)<br>23 |  |  |
| Sciatica<br>subjects affected / exposed<br>occurrences (all)   | 7 / 68 (10.29%)<br>7   |  |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)    | 12 / 68 (17.65%)<br>18 |  |  |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)             | 7 / 68 (10.29%)<br>7   |  |  |
| Gastrointestinal disorders<br>Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all) | 6 / 68 (8.82%)<br>6    |  |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)                               | 10 / 68 (14.71%)<br>11 |  |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                                     | 5 / 68 (7.35%)<br>5    |  |  |



|   |                  |  |  |
|---|------------------|--|--|
| Abdominal distension                            |                  |  |  |
| subjects affected / exposed                     | 5 / 68 (7.35%)   |  |  |
| occurrences (all)                               | 5                |  |  |
| Constipation                                    |                  |  |  |
| subjects affected / exposed                     | 10 / 68 (14.71%) |  |  |
| occurrences (all)                               | 12               |  |  |
| Diarrhoea                                       |                  |  |  |
| subjects affected / exposed                     | 16 / 68 (23.53%) |  |  |
| occurrences (all)                               | 22               |  |  |
| Dyspepsia                                       |                  |  |  |
| subjects affected / exposed                     | 23 / 68 (33.82%) |  |  |
| occurrences (all)                               | 33               |  |  |
| Gastritis                                       |                  |  |  |
| subjects affected / exposed                     | 4 / 68 (5.88%)   |  |  |
| occurrences (all)                               | 5                |  |  |
| Gastrooesophageal reflux disease                |                  |  |  |
| subjects affected / exposed                     | 10 / 68 (14.71%) |  |  |
| occurrences (all)                               | 14               |  |  |
| Nausea  |                  |  |  |
| subjects affected / exposed                     | 12 / 68 (17.65%) |  |  |
| occurrences (all)                               | 16               |  |  |
| Vomiting  |                  |  |  |
| subjects affected / exposed                     | 14 / 68 (20.59%) |  |  |
| occurrences (all)                               | 18               |  |  |
| Skin and subcutaneous tissue disorders          |                  |  |  |
| Pruritus  |                  |  |  |
| subjects affected / exposed                     | 4 / 68 (5.88%)   |  |  |
| occurrences (all)                               | 6                |  |  |
| Rash  |                  |  |  |
| subjects affected / exposed                     | 4 / 68 (5.88%)   |  |  |
| occurrences (all)                               | 5                |  |  |
| Renal and urinary disorders                     |                  |  |  |
| Renal failure                                   |                  |  |  |
| subjects affected / exposed                     | 5 / 68 (7.35%)   |  |  |
| occurrences (all)                               | 6                |  |  |
| Musculoskeletal and connective tissue disorders |                  |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| Arthralgia                  |                  |  |  |
| subjects affected / exposed | 7 / 68 (10.29%)  |  |  |
| occurrences (all)           | 9                |  |  |
| Back pain                   |                  |  |  |
| subjects affected / exposed | 8 / 68 (11.76%)  |  |  |
| occurrences (all)           | 11               |  |  |
| Muscle spasms               |                  |  |  |
| subjects affected / exposed | 9 / 68 (13.24%)  |  |  |
| occurrences (all)           | 10               |  |  |
| Musculoskeletal pain        |                  |  |  |
| subjects affected / exposed | 4 / 68 (5.88%)   |  |  |
| occurrences (all)           | 4                |  |  |
| Myalgia                     |                  |  |  |
| subjects affected / exposed | 4 / 68 (5.88%)   |  |  |
| occurrences (all)           | 4                |  |  |
| Osteoarthritis              |                  |  |  |
| subjects affected / exposed | 5 / 68 (7.35%)   |  |  |
| occurrences (all)           | 5                |  |  |
| Pain in extremity           |                  |  |  |
| subjects affected / exposed | 5 / 68 (7.35%)   |  |  |
| occurrences (all)           | 5                |  |  |
| Infections and infestations |                  |  |  |
| Gastroenteritis             |                  |  |  |
| subjects affected / exposed | 8 / 68 (11.76%)  |  |  |
| occurrences (all)           | 12               |  |  |
| Bronchitis                  |                  |  |  |
| subjects affected / exposed | 13 / 68 (19.12%) |  |  |
| occurrences (all)           | 20               |  |  |
| Gastrointestinal infection  |                  |  |  |
| subjects affected / exposed | 6 / 68 (8.82%)   |  |  |
| occurrences (all)           | 10               |  |  |
| Nasopharyngitis             |                  |  |  |
| subjects affected / exposed | 41 / 68 (60.29%) |  |  |
| occurrences (all)           | 111              |  |  |
| Influenza                   |                  |  |  |

|                                    |                  |  |  |
|------------------------------------|------------------|--|--|
| subjects affected / exposed        | 9 / 68 (13.24%)  |  |  |
| occurrences (all)                  | 20               |  |  |
| Pneumonia                          |                  |  |  |
| subjects affected / exposed        | 4 / 68 (5.88%)   |  |  |
| occurrences (all)                  | 4                |  |  |
| Sinusitis                          |                  |  |  |
| subjects affected / exposed        | 5 / 68 (7.35%)   |  |  |
| occurrences (all)                  | 9                |  |  |
| Respiratory tract infection        |                  |  |  |
| subjects affected / exposed        | 15 / 68 (22.06%) |  |  |
| occurrences (all)                  | 35               |  |  |
| Urinary tract infection            |                  |  |  |
| subjects affected / exposed        | 6 / 68 (8.82%)   |  |  |
| occurrences (all)                  | 16               |  |  |
| Metabolism and nutrition disorders |                  |  |  |
| Hypokalaemia                       |                  |  |  |
| subjects affected / exposed        | 11 / 68 (16.18%) |  |  |
| occurrences (all)                  | 13               |  |  |
| Iron deficiency                    |                  |  |  |
| subjects affected / exposed        | 4 / 68 (5.88%)   |  |  |
| occurrences (all)                  | 4                |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 17 January 2007 | After 2 subjects were enrolled, protocol was corrected for consistent requirements for biomarker samples.  |
| 28 March 2007   | 1. Further allowed concomitant medications added (and corresponding exclusion criterion deleted): calcium channel blockers given up to the dose approved for arterial hypertension, such as nifedipine up to 120 milligram per day (mg/day), diltiazem up to 360 mg/day, amlodipine up to 10 mg/day. 2. Additional laboratories for safety laboratory added due to new study centers. 3. PAPmean reduced from 30 to 25 millimeter of mercury as inclusion criterion. 4. Change in exclusion criteria: resting heart rate less than 55 beats per minute or more than 105 beats per minute. 5. Number of valid subjects to be treated increased to 25. 6. Optional openlabel extension phase introduced for subjects willing to stay on riociguat following the initial 12week treatment phase. 7. Cancellation of fasting period on Day 0. 8. Addition of troponin I as additional cardiac marker.  |
| 08 May 2007     | 1. Change of clinical phase to "clinical pharmacology study phase I/II". 2. Inclusion criteria: change of upper age limit from 65 to 75 years of age. 3. Inclusion criteria: change of upper limit of body mass index from 30 to 35 kilogram per square meter. 4. Exclusion criteria: increase of PCWP limit to >15 millimeter of mercury. 5. Correction of the Borg modified dyspnea score rating scale. 6. Shortening of final study visit procedures in subjects participating in the extension phase.  |
| 16 October 2007 | 1. Number of subjects to be treated increased to 60. 2. Interim analysis after 25 subjects completed the 12-week treatment phase. 3. Further allowed concomitant medications added (and corresponding exclusion criterion deleted): Bosentan. 4. After the availability of all data an unplanned analysis was performed including all subjects of the 12-week dose titration period to supply the most important information as soon as possible. 5. Box-Whisker-Plots are displayed instead of profile curves for PK concentrations.  |
| 29 May 2008     | 1. Supply of new riociguat tablets at doses of 1.0, 1.5, and 2.0 mg. 2. Introduction of the optional openlabel extension period to assess the longterm safety and tolerability of riociguat in subjects having completed the main study as study objective. 3. Introduction of end of optional open label extension period visit and 6-monthly follow-up. 4. Introduction of events of special interests (death, heart/lung transplantation, arterial septostomy, pulmonary endarterectomy, start of new pulmonary hypertensionspecific treatment. 5. Subjects were to be withdrawn from the study in case of use of the following medications : – Unspecific phosphodiesterase (PDE) inhibitors, such as dipyridamole, theophylline, pentoxifylline, enoximone, milrinone, or pimobendan. – Specific PDE inhibitors such as sildenafil, vardenafil, or tadalafil. – No donors, such as nitrates. 6. Introduction of additional warnings based on the results of clinical pharmacological studies: – Due to possible PK interactions between riociguat and strong cytochrome P450 3A4 inhibitors, such as ketoconazole, concomitant treatment was to be applied with caution, such as additional blood pressure monitoring. – Antacids like aluminum hydroxide/magnesium hydroxide, such as maaloxan, were not to be taken simultaneously with riociguat because a negative impact on the bioavailability of the study drug had been observed. To avoid such interaction, antacids were to be taken not before 1 hour after intake of riociguat. |

|                  |  |
|------------------|--|
| 25 March 2010    | 1. Smoking status questioning added to the protocol as riociguat clearance is increased in smokers compared to nonsmokers. 2. "Syncope" was defined as a safetyrelevant event of special interest and thus was to be reported as a serious adverse event. 3. Subject participation in another clinical trial was added as criterion for removal. 4. In the extension part of the study, the dose titration scheme was identical to that of the main study; however, in case that the 1 mg TID dose was not tolerated, the riociguat dose could be reduced to a minimum dose of 0.5 mg TID.   |
| 13 December 2012 | 1. Optional Open Label Extension Period (OOLEP) procedures were changed to facilitate studyrelated activities as follows: A separate subject information and informed consent form was added and was signed by all subjects participating in this period. Deviation of +/-14 days from the scheduled every 3 months visit added as permissible. Every 3 months visits no longer required smoking status, but a physical exam was performed and status of concomitant medication was determined 1 hour before study treatment. Laboratory sampling and electrocardiogram (ECG) were only to be performed locally at the investigator's discretion. Vital signs, modified Borg dyspnea score, PK sampling, and AE questioning were reduced. Return of all unused medication by the subject and dispensing of a 3-month supply of study medication was performed. The End of OOLEP Visit was 30 (+5) days after the last dose. WHO functional class, 6MWT, ECG, safety laboratory, troponin I, prohormone, modified Borg dyspnea score, and smoking status were no longer required at this visit; physical exam results, heart rate and blood pressure, and pregnancy test data if applicable were captured, and AEs and events of special interest were documented. Subjects who permanently stopped riociguat in the OOLEP due to reasons other than consent withdrawal were no longer required to be followed up; subjects were to return to the hospital for the End of OOLEP Visit. 2. ECG and laboratory test abnormalities as well as change in modified Borg dyspnea score was not to be analyzed due to data for these procedures in this trial period no longer being captured. 3. Premature termination of study or closure of center criterion added: "If subjects can be transferred to another trial or therapy program with riociguat which ensures that subjects benefit can be treated until the drug receives official approval and will be commercially available." 4. A routine right heart catheterization was considered. |
| 03 April 2013    | After all subjects had already been enrolled, the following changes were made which concerned the Optional Extension Period and End of Open Label Extension Period Visit: 1. Recording of events of special interest (death, heart/lung transplantation, atrial septostomy, pulmonary endarterectomy, start of new PH specific treatment [endothelin antagonists, prostacyclin analogues, PDE type 5-inhibitors]) in this period was clarified as "With the exception of death (to be recorded on the end of study page), the first occurrence of each of the events of special interest was to be captured at each visit of the optional open label extension period and end of open label extension period visit (safety visit)". 2. For the estimation of the combined endpoint "time to clinical worsening" in this period, the following clarifications were added: the first occurrence of events of special interest was to be considered and incidence tables of the overall rate were to be presented, together with the Kaplan-Meier survival curve. 3. Safety analyses in this period were clarified as "change-from-baseline analyses".  |

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.

Decimal places were automatically truncated if last decimal equals zero.

Notes: