



## Clinical trial results:

**Long term, multicenter, single-arm, open-label extension study of the MERIT-1 study, to assess the safety, tolerability and efficacy of macitentan in subjects with inoperable chronic thromboembolic pulmonary hypertension (CTEPH)**

### Summary

|                          |                            |
|--------------------------|----------------------------|
| EudraCT number           | 2013-003457-25             |
| Trial protocol           | CZ BE GB HU DE AT NL LT FR |
| Global end of trial date | 21 March 2022              |

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 02 April 2023 |
| First version publication date | 02 April 2023 |

### Trial information

#### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | AC-055E202 |
|-----------------------|------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02060721 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Actelion Pharmaceuticals Ltd.   |
| Sponsor organisation address | Gewerbestrass 16, Allschwil, Switzerland, 4123  |
| Public contact               | Clinical Registry Group, Actelion Pharmaceuticals Ltd.,<br>ClinicalTrialsEU@its.jnj.com |
| Scientific contact           | Clinical Registry Group, Actelion Pharmaceuticals Ltd.,<br>ClinicalTrialsEU@its.jnj.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                       | 21 March 2022 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 21 March 2022 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the long-term safety and tolerability of macitentan 10 milligrams (mg) in subjects with inoperable CTEPH.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 03 February 2015 |
| 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 | Belgium: 1             |
| Country: Number of subjects enrolled | China: 23              |
| Country: Number of subjects enrolled | Czechia: 2             |
| Country: Number of subjects enrolled | Germany: 3             |
| Country: Number of subjects enrolled | France: 3              |
| Country: Number of subjects enrolled | United Kingdom: 3      |
| Country: Number of subjects enrolled | Hungary: 4             |
| Country: Number of subjects enrolled | Lithuania: 2           |
| Country: Number of subjects enrolled | Mexico: 2              |
| Country: Number of subjects enrolled | Poland: 3              |
| Country: Number of subjects enrolled | Russian Federation: 20 |
| Country: Number of subjects enrolled | Thailand: 4            |
| Country: Number of subjects enrolled | Turkey: 2              |
| Country: Number of subjects enrolled | Ukraine: 4             |
| Worldwide total number of subjects   | 76                     |
| EEA total number of subjects         | 18                     |

Notes:

**Subjects enrolled per age group**

|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 48 |
| From 65 to 84 years                       | 28 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 76 subjects who completed the double-blind MERIT-1 study, rolled-over to this study (MERIT-2), out of which 38 subjects completed the study.

### Period 1

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

### Arms

|           |                               |
|-----------|-------------------------------|
| Arm title | Macitentan 10 milligrams (mg) |
|-----------|-------------------------------|

Arm description:

Eligible subjects who were either randomised to macitentan 10 mg or placebo group during 24 weeks double-blind MERIT-1 (2013-002950-56) study, were rolled-over to this open-label extension study and received macitentan 10 mg tablet orally once daily starting from Day 1 to the end of treatment (treatment exposure ranged from 1 to 82 months).

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

Dosage and administration details:

Macitentan 10 mg tablet was administered orally once daily starting from Day 1 to the end of treatment (treatment exposure ranged from 1 to 82 months).

| Number of subjects in period 1                      | Macitentan 10 milligrams (mg) |
|---|-------------------------------|
| Started   | 76                            |
| Completed   | 38                            |
| Not completed                                       | 38                            |
| Adverse event, serious fatal                        | 14                            |
| Physician decision                                  | 2                             |
| Consent withdrawn by subject                        | 2                             |
| Compliance with local regulation: enrolled in China | 19                            |
| Lost to follow-up                                   | 1                             |

## Baseline characteristics

### Reporting groups

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Macitentan 10 milligrams (mg) |
|-----------------------|-------------------------------|

Reporting group description:

Eligible subjects who were either randomised to macitentan 10 mg or placebo group during 24 weeks double-blind MERIT-1 (2013-002950-56) study, were rolled-over to this open-label extension study and received macitentan 10 mg tablet orally once daily starting from Day 1 to the end of treatment (treatment exposure ranged from 1 to 82 months).

| Reporting group values                      | Macitentan 10 milligrams (mg) | Total |  |
|---|-------------------------------|-------|--|
| Number of subjects                          | 76                            | 76    |  |
| Title for AgeCategorical<br>Units: subjects |                               |       |  |
| Children (2-11 years)                       | 0                             | 0     |  |
| Adolescents (12-17 years)                   | 0                             | 0     |  |
| Adults (18-64 years)                        | 48                            | 48    |  |
| From 65 to 84 years                         | 28                            | 28    |  |
| 85 years and over                           | 0                             | 0     |  |
| Title for AgeContinuous<br>Units: years     |                               |       |  |
| arithmetic mean                             | 57.8                          |       |  |
| standard deviation                          | ± 13.99                       | -     |  |
| Title for Gender<br>Units: subjects         |                               |       |  |
| Female                                      | 48                            | 48    |  |
| Male  | 28                            | 28    |  |

## End points

### End points reporting groups

|  |                               |
|--|-------------------------------|
| Reporting group title  | Macitentan 10 milligrams (mg) |
| Reporting group description:<br>Eligible subjects who were either randomised to macitentan 10 mg or placebo group during 24 weeks double-blind MERIT-1 (2013-002950-56) study, were rolled-over to this open-label extension study and received macitentan 10 mg tablet orally once daily starting from Day 1 to the end of treatment (treatment exposure ranged from 1 to 82 months). |                               |

### Primary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

|                 |  |
|-----------------|--|
| End point title | Number of Subjects With Treatment-emergent Adverse Events (TEAEs) <sup>[1]</sup> |
|-----------------|--|

End point description:

An adverse event (AE) is any untoward medical occurrence in a subject participating in a clinical study that does not necessarily have a causal relationship with the pharmaceutical/ biological agent under study. TEAEs are those events that started after administration of the first dose and up to safety follow-up visit/end of study, that is, 30 days after the last dose of study medication. Open-label analysis set (OLAS) included all data from subjects who were enrolled into this open-label extension study, from the time they entered this open-label extension study.

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

End point timeframe:

Up to 30 days after study treatment discontinuation (treatment exposure ranged from 1 to 82 months)

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: Only descriptive statistics were reported. No inferential statistics was planned.

|                             |                               |  |  |  |
|-----------------------------|-------------------------------|--|--|--|
| <b>End point values</b>     | Macitentan 10 milligrams (mg) |  |  |  |
| Subject group type          | Reporting group               |  |  |  |
| Number of subjects analysed | 76                            |  |  |  |
| Units: Subjects             | 72                            |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With AEs Leading to Study Drug Discontinuation

|                 |  |
|-----------------|--|
| End point title | Number of Subjects With AEs Leading to Study Drug Discontinuation <sup>[2]</sup> |
|-----------------|--|

End point description:

Number of subjects with AEs leading to study drug discontinuation was reported. OLAS included all data from subjects who were enrolled into this open-label extension study, from the time they entered this open-label extension study.

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

End point timeframe:

Up to 30 days after study treatment discontinuation (treatment exposure ranged from 1 to 82 months)

Notes:

[2] - 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: Only descriptive statistics were reported. No inferential statistics was planned.

|                             |                               |  |  |  |
|-----------------------------|-------------------------------|--|--|--|
| <b>End point values</b>     | Macitentan 10 milligrams (mg) |  |  |  |
| Subject group type          | Reporting group               |  |  |  |
| Number of subjects analysed | 76                            |  |  |  |
| Units: Subjects             | 9                             |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Subjects With Treatment-emergent Serious Adverse Events (SAEs)

|                 |   |
|-----------------|---|
| End point title | Number of Subjects With Treatment-emergent Serious Adverse Events (SAEs) <sup>[3]</sup> |
|-----------------|---|

End point description:

A serious adverse event (SAE) is any untoward medical occurrence that at any dose resulting in any of following outcomes: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a suspected transmission of any infectious agent via a medicinal product. Treatment-emergent SAEs were those events that started after administration of the first dose and up to safety follow-up visit/end of study, that is, 30 days after the last dose of study medication. OLAS included all data from subjects who were enrolled into this open-label extension study, from the time they entered this open-label extension study.

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

End point timeframe:

Up to 30 days after study treatment discontinuation (treatment exposure ranged from 1 to 82 months)

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: Only descriptive statistics were reported. No inferential statistics was planned.

|                             |                               |  |  |  |
|-----------------------------|-------------------------------|--|--|--|
| <b>End point values</b>     | Macitentan 10 milligrams (mg) |  |  |  |
| Subject group type          | Reporting group               |  |  |  |
| Number of subjects analysed | 76                            |  |  |  |
| Units: Subjects             | 44                            |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Subjects With Hemoglobin Abnormalities

|                 |   |
|-----------------|---|
| End point title | Number of Subjects With Hemoglobin Abnormalities <sup>[4]</sup> |
|-----------------|---|

**End point description:**

Number of subjects with hemoglobin abnormalities were reported. It included hemoglobin less than (<) 80 grams per litre (g/L), hemoglobin <100 g/L, hemoglobin greater than or equal to (>=) 80 g/L and <100 g/L, hemoglobin <100g/L and a decrease of >20 g/L from baseline, decrease of >20 g/L in hemoglobin from baseline, decrease of >20 g/L and <=50 g/L in hemoglobin from baseline, and decrease of >50 g/L in hemoglobin from baseline. OLAS included all data from subjects who were enrolled into this open-label extension study, from the time they entered this open-label extension study.

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

**End point timeframe:**

Up to 30 days after study treatment discontinuation (treatment exposure ranged from 1 to 82 months)

**Notes:**

[4] - 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: Only descriptive statistics were reported. No inferential statistics was planned.

| End point values                                | Macitentan 10 milligrams (mg) |  |  |  |
|---|-------------------------------|--|--|--|
| Subject group type                              | Reporting group               |  |  |  |
| Number of subjects analysed                     | 76                            |  |  |  |
| Units: Subjects                                 |                               |  |  |  |
| Hemoglobin < 80 g/L                             | 0                             |  |  |  |
| Hemoglobin <100 g/L                             | 7                             |  |  |  |
| Hemoglobin >= 80 g/L and <100 g/L               | 7                             |  |  |  |
| <100 g/L and a decrease from baseline >20 g/L   | 6                             |  |  |  |
| Decrease of >20 g/L in hemoglobin from baseline | 32                            |  |  |  |
| Decrease of >20 g/L and <=50 g/L from baseline  | 31                            |  |  |  |
| Decrease of >50 g/L in hemoglobin from baseline | 5                             |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Primary: Number of Subjects With Liver Tests Abnormalities**

|                 |  |
|-----------------|--|
| End point title | Number of Subjects With Liver Tests Abnormalities <sup>[5]</sup> |
|-----------------|--|

**End point description:**

Number of subjects with liver tests abnormalities were reported. It included alanine aminotransferase (ALT) or aspartate aminotransferase (AST): >=3 x Upper limit of the normal range (ULN), >=3 and <5 x ULN, >=5 ULN, and >=5 and <8 x ULN, >= 8 x ULN, and total bilirubin >=2 x ULN. OLAS included all data from subjects who were enrolled into this open-label extension study, from the time they entered this open-label extension study.

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

**End point timeframe:**

Up to 30 days after study treatment discontinuation (treatment exposure ranged from 1 to 82 months)

**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: Only descriptive statistics were reported. No inferential statistics was planned.



|  |                               |  |  |  |
|--|-------------------------------|--|--|--|
| <b>End point values</b>                  | Macitentan 10 milligrams (mg) |  |  |  |
| Subject group type                       | Reporting group               |  |  |  |
| Number of subjects analysed              | 76                            |  |  |  |
| Units: Subjects                          |                               |  |  |  |
| ALT or AST $\geq 3 \times$ ULN           | 2                             |  |  |  |
| ALT or AST $\geq 3$ and $< 5 \times$ ULN | 1                             |  |  |  |
| ALT or AST $\geq 5 \times$ ULN           | 1                             |  |  |  |
| ALT or AST $\geq 5$ and $< 8 \times$ ULN | 0                             |  |  |  |
| ALT or AST $\geq 8 \times$ ULN           | 1                             |  |  |  |
| Total Bilirubin $\geq 2 \times$ ULN      | 8                             |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Change from Baseline in Blood Pressure at Month 6

|  |  |
|--|--|
| End point title  | Change from Baseline in Blood Pressure at Month 6 <sup>[6]</sup> |
| End point description:   |  |
| Change from baseline in blood pressure (both systolic blood pressure [SBP] and diastolic blood pressure [DBP]) at Month 6 was reported. OLAS included all data from subjects who were enrolled into this open-label extension study, from the time they entered this open-label extension study. Here, 'N' (number of subjects analysed) signifies subjects evaluated for this endpoint. |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| Baseline and Month 6   |  |
| Notes:   |  |
| [6] - 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: Only descriptive statistics were reported. No inferential statistics was planned.   |  |

|                                      |                               |  |  |  |
|--------------------------------------|-------------------------------|--|--|--|
| <b>End point values</b>              | Macitentan 10 milligrams (mg) |  |  |  |
| Subject group type                   | Reporting group               |  |  |  |
| Number of subjects analysed          | 70                            |  |  |  |
| Units: Millimetres of mercury (mmHg) |                               |  |  |  |
| arithmetic mean (standard deviation) |                               |  |  |  |
| SBP                                  | -0.4 ( $\pm 13.15$ )          |  |  |  |
| DBP                                  | -2.8 ( $\pm 9.51$ )           |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Change from Baseline in Pulse Rate at Month 6

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Pulse Rate at Month 6 <sup>[7]</sup> |
|-----------------|--|

End point description:

Change from baseline in pulse rate at Month 6 was reported. OLAS included all data from subjects who were enrolled into this open-label extension study, from the time they entered this open-label extension study. Here, 'N' (number of subjects analysed) signifies subjects evaluated for this endpoint.

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

End point timeframe:

Baseline and Month 6

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: Only descriptive statistics were reported. No inferential statistics was planned.

| End point values                     | Macitentan 10 milligrams (mg) |  |  |  |
|--------------------------------------|-------------------------------|--|--|--|
| Subject group type                   | Reporting group               |  |  |  |
| Number of subjects analysed          | 70                            |  |  |  |
| Units: Beats per minute              |                               |  |  |  |
| arithmetic mean (standard deviation) | -1.1 (± 8.76)                 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Change from Baseline in Body Weight at Month 6

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in Body Weight at Month 6 <sup>[8]</sup> |
|-----------------|---|

End point description:

Change from baseline in body weight at Month 6 was reported. OLAS included all data from subjects who were enrolled into this open-label extension study, from the time they entered this open-label extension study. Here, 'N' (number of subjects analysed) signifies subjects evaluated for this endpoint.

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

End point timeframe:

Baseline and Month 6

Notes:

[8] - 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: Only descriptive statistics were reported. No inferential statistics was planned.

| End point values                     | Macitentan 10 milligrams (mg) |  |  |  |
|--------------------------------------|-------------------------------|--|--|--|
| Subject group type                   | Reporting group               |  |  |  |
| Number of subjects analysed          | 70                            |  |  |  |
| Units: kilograms (kg)                |                               |  |  |  |
| arithmetic mean (standard deviation) | -0.35 (± 2.871)               |  |  |  |

## Statistical analyses



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 30 days after study treatment discontinuation (treatment exposure ranged from 1 to 82 months)

Adverse event reporting additional description:

Open-label analysis set (OLAS) included all data from subjects who were enrolled into this open-label extension study, from the time they entered this open-label extension study.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

### Reporting groups

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Macitentan 10 milligrams (mg) |
|-----------------------|-------------------------------|

Reporting group description:

Eligible subjects who were either randomised to macitentan 10 mg or placebo group during 24 weeks double-blind MERIT-1 (2013-002950-56) study, were rolled-over to this open-label extension study and received macitentan 10 mg tablet orally once daily starting from Day 1 to the end of treatment (treatment exposure ranged from 1 to 82 months).

| Serious adverse events  | Macitentan 10 milligrams (mg) |  |  |
|---|-------------------------------|--|--|
| Total subjects affected by serious adverse events                   |                               |  |  |
| subjects affected / exposed   | 44 / 76 (57.89%)              |  |  |
| number of deaths (all causes)                                       | 14                            |  |  |
| number of deaths resulting from adverse events                      |                               |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                               |  |  |
| Basal Cell Carcinoma  |                               |  |  |
| subjects affected / exposed   | 1 / 76 (1.32%)                |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                         |  |  |
| deaths causally related to treatment / all                          | 0 / 0                         |  |  |
| Breast Cancer   |                               |  |  |
| subjects affected / exposed   | 1 / 76 (1.32%)                |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                         |  |  |
| deaths causally related to treatment / all                          | 0 / 0                         |  |  |
| Gastric Cancer Stage Iv   |                               |  |  |
| subjects affected / exposed   | 1 / 76 (1.32%)                |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                         |  |  |
| deaths causally related to treatment / all                          | 0 / 0                         |  |  |
| Breast Cancer Metastatic  |                               |  |  |

|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                          | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Vascular disorders                                   |                |  |  |
| Hypotension  |                |  |  |
| subjects affected / exposed                          | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Air Embolism   |                |  |  |
| subjects affected / exposed                          | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Reperfusion Injury                                   |                |  |  |
| subjects affected / exposed                          | 2 / 76 (2.63%) |  |  |
| occurrences causally related to treatment / all      | 0 / 3          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Surgical and medical procedures                      |                |  |  |
| Angioplasty  |                |  |  |
| subjects affected / exposed                          | 3 / 76 (3.95%) |  |  |
| occurrences causally related to treatment / all      | 0 / 10         |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Arterial Angioplasty                                 |                |  |  |
| subjects affected / exposed                          | 7 / 76 (9.21%) |  |  |
| occurrences causally related to treatment / all      | 0 / 23         |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Pulmonary Endarterectomy                             |                |  |  |
| subjects affected / exposed                          | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Death  |                |  |  |
| subjects affected / exposed                          | 3 / 76 (3.95%) |  |  |
| occurrences causally related to treatment / all      | 0 / 3          |  |  |
| deaths causally related to treatment / all           | 0 / 3          |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| General Physical Health Deterioration           |                |  |  |  |
| subjects affected / exposed                     | 2 / 76 (2.63%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Peripheral Swelling                             |                |  |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Multiple Organ Dysfunction Syndrome             |                |  |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |  |
| Pyrexia   |                |  |  |  |
| subjects affected / exposed                     | 2 / 76 (2.63%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |  |
| Acute Respiratory Failure                       |                |  |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Asthma  |                |  |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Dyspnoea  |                |  |  |  |
| subjects affected / exposed                     | 2 / 76 (2.63%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Haemoptysis                                     |                |  |  |  |
| subjects affected / exposed                     | 2 / 76 (2.63%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Hypercapnia                                     |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Obstructive Airways Disorder                    |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pickwickian Syndrome                            |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pulmonary Embolism                              |                |  |  |
| subjects affected / exposed                     | 3 / 76 (3.95%) |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 2          |  |  |
| Sleep Apnoea Syndrome                           |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pulmonary Hypertension                          |                |  |  |
| subjects affected / exposed                     | 6 / 76 (7.89%) |  |  |
| occurrences causally related to treatment / all | 0 / 6          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Investigations                                  |                |  |  |
| Catheterisation Cardiac                         |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Chest X-Ray Abnormal                            |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Haemoglobin Decreased                           |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Injury, poisoning and procedural complications  |                |  |  |
| Head Injury                                     |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Fall  |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Chemical Burns of Eye                           |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Lumbar Vertebral Fracture                       |                |  |  |
| subjects affected / exposed                     | 3 / 76 (3.95%) |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Congenital, familial and genetic disorders      |                |  |  |
| Arteriovenous Malformation                      |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac disorders                               |                |  |  |
| Acute Myocardial Infarction                     |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Angina Pectoris                                 |                |  |  |



|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Aortic Valve Stenosis                           |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Atrial Fibrillation                             |                |  |  |
| subjects affected / exposed                     | 2 / 76 (2.63%) |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Atrial Flutter                                  |                |  |  |
| subjects affected / exposed                     | 2 / 76 (2.63%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Atrial Tachycardia                              |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac Arrest                                  |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Cardiac Failure                                 |                |  |  |
| subjects affected / exposed                     | 4 / 76 (5.26%) |  |  |
| occurrences causally related to treatment / all | 0 / 9          |  |  |
| deaths causally related to treatment / all      | 0 / 3          |  |  |
| Right Ventricular Failure                       |                |  |  |
| subjects affected / exposed                     | 5 / 76 (6.58%) |  |  |
| occurrences causally related to treatment / all | 0 / 8          |  |  |
| deaths causally related to treatment / all      | 0 / 2          |  |  |
| Coronary Artery Disease                         |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac Failure Congestive                      |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac Failure Acute                           |                |  |  |
| subjects affected / exposed                     | 3 / 76 (3.95%) |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 3          |  |  |
| Nervous system disorders                        |                |  |  |
| Haemorrhage Intracranial                        |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Diplegia  |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Ear and labyrinth disorders                     |                |  |  |
| Deafness Neurosensory                           |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Eye disorders                                   |                |  |  |
| Cataract  |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Vision Blurred                                  |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|  |   |                |  |  |
|--|---|----------------|--|--|
| Gastrointestinal disorders<br>Abdominal Pain | subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
|  | occurrences causally related to treatment / all | 0 / 2          |  |  |
|  | deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastric Polyps                               | subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
|  | occurrences causally related to treatment / all | 0 / 1          |  |  |
|  | deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal Motility Disorder           | subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
|  | occurrences causally related to treatment / all | 0 / 1          |  |  |
|  | deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pancreatitis Acute                           | subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
|  | occurrences causally related to treatment / all | 0 / 1          |  |  |
|  | deaths causally related to treatment / all      | 0 / 0          |  |  |
| Large Intestine Polyp                        | subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
|  | occurrences causally related to treatment / all | 0 / 1          |  |  |
|  | deaths causally related to treatment / all      | 0 / 0          |  |  |
| Peritoneal Adhesions                         | subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
|  | occurrences causally related to treatment / all | 0 / 1          |  |  |
|  | deaths causally related to treatment / all      | 0 / 0          |  |  |
| Vomiting                                     | subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
|  | occurrences causally related to treatment / all | 0 / 1          |  |  |
|  | deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hepatobiliary disorders<br>Hepatitis         | subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
|  | occurrences causally related to treatment / all | 0 / 1          |  |  |
|  | deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Renal and urinary disorders                     |                |  |  |
| Haematuria                                      |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal Failure                                   |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Systemic Lupus Erythematosus                    |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Appendicitis                                    |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Appendiceal Abscess                             |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Covid-19 Pneumonia                              |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumonia Parainfluenzae Viral                  |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumonia                                       |                |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| subjects affected / exposed                     | 4 / 76 (5.26%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 5          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Neutropenic Sepsis                              |                |  |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |  |
| Pulmonary Tuberculosis                          |                |  |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pyelonephritis Acute                            |                |  |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pyelonephritis Chronic                          |                |  |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Respiratory Tract Infection                     |                |  |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |  |
| Sepsis  |                |  |  |  |
| subjects affected / exposed                     | 2 / 76 (2.63%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Septic Shock                                    |                |  |  |  |
| subjects affected / exposed                     | 2 / 76 (2.63%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |  |
| Streptococcal Sepsis                            |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Metabolism and nutrition disorders              |                |  |  |
| Hypernatraemia                                  |                |  |  |
| subjects affected / exposed                     | 1 / 76 (1.32%) |  |  |
| 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>                     | Macitentan 10 milligrams (mg) |  |  |
| Total subjects affected by non-serious adverse events |                               |  |  |
| subjects affected / exposed                           | 67 / 76 (88.16%)              |  |  |
| Investigations  |                               |  |  |
| Blood Bilirubin Increased                             |                               |  |  |
| subjects affected / exposed                           | 5 / 76 (6.58%)                |  |  |
| occurrences (all)                                     | 6                             |  |  |
| Blood Creatinine Increased                            |                               |  |  |
| subjects affected / exposed                           | 4 / 76 (5.26%)                |  |  |
| occurrences (all)                                     | 4                             |  |  |
| C-Reactive Protein Increased                          |                               |  |  |
| subjects affected / exposed                           | 6 / 76 (7.89%)                |  |  |
| occurrences (all)                                     | 6                             |  |  |
| Haemoglobin Decreased                                 |                               |  |  |
| subjects affected / exposed                           | 13 / 76 (17.11%)              |  |  |
| occurrences (all)                                     | 17                            |  |  |
| Weight Decreased                                      |                               |  |  |
| subjects affected / exposed                           | 7 / 76 (9.21%)                |  |  |
| occurrences (all)                                     | 8                             |  |  |
| Cardiac disorders                                     |                               |  |  |
| Cardiac Failure                                       |                               |  |  |
| subjects affected / exposed                           | 5 / 76 (6.58%)                |  |  |
| occurrences (all)                                     | 5                             |  |  |
| Nervous system disorders                              |                               |  |  |

|  |                        |  |  |
|--|------------------------|--|--|
| Headache<br>subjects affected / exposed<br>occurrences (all)   | 7 / 76 (9.21%)<br>10   |  |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)  | 8 / 76 (10.53%)<br>15  |  |  |
| Syncope<br>subjects affected / exposed<br>occurrences (all)  | 7 / 76 (9.21%)<br>8    |  |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)                    | 10 / 76 (13.16%)<br>11 |  |  |
| General disorders and administration<br>site conditions<br>Pyrexia<br>subjects affected / exposed<br>occurrences (all) | 4 / 76 (5.26%)<br>5    |  |  |
| Oedema Peripheral<br>subjects affected / exposed<br>occurrences (all)  | 11 / 76 (14.47%)<br>13 |  |  |
| Eye disorders<br>Cataract<br>subjects affected / exposed<br>occurrences (all)  | 6 / 76 (7.89%)<br>7    |  |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                            | 7 / 76 (9.21%)<br>11   |  |  |
| Respiratory, thoracic and mediastinal<br>disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)        | 9 / 76 (11.84%)<br>11  |  |  |
| Haemoptysis<br>subjects affected / exposed<br>occurrences (all)  | 4 / 76 (5.26%)<br>7    |  |  |
| Dyspnoea   |                        |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 7 / 76 (9.21%)   |  |  |
| occurrences (all)                               | 7                |  |  |
| Pulmonary Hypertension                          |                  |  |  |
| subjects affected / exposed                     | 11 / 76 (14.47%) |  |  |
| occurrences (all)                               | 12               |  |  |
| Musculoskeletal and connective tissue disorders |                  |  |  |
| Osteoarthritis                                  |                  |  |  |
| subjects affected / exposed                     | 5 / 76 (6.58%)   |  |  |
| occurrences (all)                               | 5                |  |  |
| Back Pain                                       |                  |  |  |
| subjects affected / exposed                     | 7 / 76 (9.21%)   |  |  |
| occurrences (all)                               | 7                |  |  |
| Arthralgia                                      |                  |  |  |
| subjects affected / exposed                     | 6 / 76 (7.89%)   |  |  |
| occurrences (all)                               | 9                |  |  |
| Pain in Extremity                               |                  |  |  |
| subjects affected / exposed                     | 6 / 76 (7.89%)   |  |  |
| occurrences (all)                               | 6                |  |  |
| Infections and infestations                     |                  |  |  |
| Bronchitis                                      |                  |  |  |
| subjects affected / exposed                     | 9 / 76 (11.84%)  |  |  |
| occurrences (all)                               | 14               |  |  |
| Respiratory Tract Infection Viral               |                  |  |  |
| subjects affected / exposed                     | 4 / 76 (5.26%)   |  |  |
| occurrences (all)                               | 4                |  |  |
| Nasopharyngitis                                 |                  |  |  |
| subjects affected / exposed                     | 9 / 76 (11.84%)  |  |  |
| occurrences (all)                               | 15               |  |  |
| Covid-19  |                  |  |  |
| subjects affected / exposed                     | 6 / 76 (7.89%)   |  |  |
| occurrences (all)                               | 7                |  |  |
| Urinary Tract Infection                         |                  |  |  |
| subjects affected / exposed                     | 7 / 76 (9.21%)   |  |  |
| occurrences (all)                               | 14               |  |  |
| Upper Respiratory Tract Infection               |                  |  |  |



|  |                        |  |  |
|--|------------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 12 / 76 (15.79%)<br>21 |  |  |
| Metabolism and nutrition disorders               |                        |  |  |
| Hypokalaemia                                     |                        |  |  |
| subjects affected / exposed                      | 4 / 76 (5.26%)         |  |  |
| occurrences (all)                                | 8                      |  |  |
| Hyperuricaemia                                   |                        |  |  |
| subjects affected / exposed                      | 4 / 76 (5.26%)         |  |  |
| occurrences (all)                                | 4                      |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 15 July 2020      | The purpose of this amendment was to update the study specific criteria for drug interruption/ permanent discontinuation and forbidden concomitant medication sections to prohibit strong Cytochrome P-450 (CYP) 3A4 inhibitors, moderate dual CYP3A4/CYP2C9 inhibitors, and concomitant administration of moderate CYP3A4 and CYP2C9 inhibitors.        |
| 28 September 2020 | The purpose of this amendment was to update the description of the investigational medicinal product used in this study from debossed on one side to debossed on either one or both sides.   |
| 22 June 2021      | The purpose of this amendment was to clarify how to manage the roll-over of MERIT-2 subjects into a continued access program (post-trial access program or other open-label extension study). In addition, the forbidden concomitant medications section was updated to clarify that macitentan 10 mg is not considered as an investigational treatment. |

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.

Study limitations included the open-label (OL), uncontrolled design, and small sample size.

Notes: