



Clinical trial results:

A Multi-center, Double-blind, Placebo-controlled Phase 2b Study to Evaluate the Efficacy and Safety of Macitentan in Subjects with Heart Failure with Preserved Ejection Fraction and Pulmonary Vascular Disease

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2016-003653-15 |
| Trial protocol | DE HU GB DK CZ AT SE ES BG |
| Global end of trial date | 12 March 2021 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 24 March 2022 |
| First version publication date | 24 March 2022 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | AC-055G202 |
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Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03153111 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Actelion Pharmaceuticals Ltd |
| Sponsor organisation address | Gewerbestrasse 16, Allschwil, Switzerland, CH-4123 |
| Public contact | Clinical Registry group, Actelion Pharmaceuticals Ltd, ClinicalTrialsEU@its.jnj.com |
| Scientific contact | Clinical Registry group, Actelion Pharmaceuticals Ltd, 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 | 12 March 2021 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|---------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 12 March 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate whether macitentan 10 milligrams (mg) reduced N-terminal pro-brain natriuretic peptide (NT-proBNP) versus placebo at Week 24 in subjects with heart failure with preserved ejection fraction (HFpEF) and pulmonary vascular disease (PVD).

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 Practice (GCP) and applicable regulatory requirements. Safety assessments included analysis of treatment-emergent adverse events (TEAEs), laboratory analyte values, vital sign measurements, electrocardiogram (ECG) data, all-cause hospital admissions up to 30 days after treatment, estimated Glomerular Filtration Rate (GFR), and heart failure (HF) signs/symptoms of special interest reported during the study.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 02 August 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 1 |
| Country: Number of subjects enrolled | Austria: 2 |
| Country: Number of subjects enrolled | Bulgaria: 10 |
| Country: Number of subjects enrolled | Brazil: 2 |
| Country: Number of subjects enrolled | Czechia: 3 |
| Country: Number of subjects enrolled | Germany: 13 |
| Country: Number of subjects enrolled | Denmark: 2 |
| Country: Number of subjects enrolled | Spain: 1 |
| Country: Number of subjects enrolled | France: 6 |
| Country: Number of subjects enrolled | United Kingdom: 5 |
| Country: Number of subjects enrolled | Hungary: 9 |
| Country: Number of subjects enrolled | Israel: 27 |
| Country: Number of subjects enrolled | Poland: 8 |
| Country: Number of subjects enrolled | Romania: 7 |
| Country: Number of subjects enrolled | Russian Federation: 20 |
| Country: Number of subjects enrolled | Sweden: 2 |
| Country: Number of subjects enrolled | United States: 24 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 142 |
| EEA total number of subjects | 63 |

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) | 18 |
| From 65 to 84 years | 112 |
| 85 years and over | 12 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Out of 143 randomised subjects, 1 subject was randomised by mistake and did not receive any dose of study drug. 142 subjects received the study drug and were analysed.

Period 1

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

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Subjects received placebo tablet orally once a day starting from Day 1 up to Week 52.

| | |
|--|----------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo tablet was administered orally once a day starting at Day 1 up to Week 52.

| | |
|------------------|------------|
| Arm title | Macitentan |
|------------------|------------|

Arm description:

Subjects received macitentan 10 milligrams (mg) tablet orally once a day starting from Day 1 up to Week 52.

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

Dosage and administration details:

Macitentan 10 mg tablet was administered orally once a day starting at Day 1 up to Week 52.

| Number of subjects in period 1 | Placebo | Macitentan |
|---------------------------------------|---------|------------|
| Started | 71 | 71 |
| Completed | 62 | 60 |
| Not completed | 9 | 11 |
| Adverse event, serious fatal | 5 | 2 |
| Consent withdrawn by subject | 3 | 1 |
| Physician decision | - | 1 |
| Adverse event, non-fatal | - | 2 |
| Adverse event, serious non-fatal | 1 | 4 |
| Lost to follow-up | - | 1 |

Baseline characteristics

Reporting groups

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

Reporting group description:

Subjects received placebo tablet orally once a day starting from Day 1 up to Week 52.

| | |
|-----------------------|------------|
| Reporting group title | Macitentan |
|-----------------------|------------|

Reporting group description:

Subjects received macitentan 10 milligrams (mg) tablet orally once a day starting from Day 1 up to Week 52.

| Reporting group values | Placebo | Macitentan | Total |
|---|---------|------------|-------|
| Number of subjects | 71 | 71 | 142 |
| Title for AgeCategorical Units: subjects | | | |
| Adults (18-64 years) | 8 | 10 | 18 |
| From 65 to 84 years | 57 | 55 | 112 |
| 85 years and over | 6 | 6 | 12 |
| Title for AgeContinuous Units: years | | | |
| arithmetic mean | 74.2 | 72.9 | |
| standard deviation | ± 8.25 | ± 10.11 | - |
| Title for Gender Units: subjects | | | |
| Female | 41 | 46 | 87 |
| Male | 30 | 25 | 55 |

End points

End points reporting groups

| | |
|---|------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects received placebo tablet orally once a day starting from Day 1 up to Week 52. | |
| Reporting group title | Macitentan |
| Reporting group description: | |
| Subjects received macitentan 10 milligrams (mg) tablet orally once a day starting from Day 1 up to Week 52. | |

Primary: Percent of Baseline N-terminal Pro-brain Natriuretic Peptide (NT-proBNP) Assessed at Week 24

| | |
|---|--|
| End point title | Percent of Baseline N-terminal Pro-brain Natriuretic Peptide (NT-proBNP) Assessed at Week 24 |
| End point description: | |
| Percent of baseline NT-proBNP assessed at week 24 was reported. Percent of baseline is calculated as the ratio of the Week 24 NT-proBNP value over baseline value, expressed in percentage. NT-proBNP is one of the best established cardiovascular response markers among all available surrogates in heart failure (HF). Full analysis set (FAS) included subjects which were randomized to double-blind study treatment. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline and Week 24 | |

| End point values | Placebo | Macitentan | | |
|---|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 71 | 71 | | |
| Units: percentage of baseline NT-proBNP | | | | |
| geometric mean (geometric coefficient of variation) | 106.27 (\pm 0.55) | 108.39 (\pm 0.65) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis for Double-blind period |
| Comparison groups | Placebo v Macitentan |
| Number of subjects included in analysis | 142 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7923 |
| Method | ANCOVA |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 1.02 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.88 |
| upper limit | 1.19 |

Secondary: Change from Baseline to Week 24 in the Clinical Summary Score Assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ) Score

| | |
|-----------------|---|
| End point title | Change from Baseline to Week 24 in the Clinical Summary Score Assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ) Score |
|-----------------|---|

End point description:

The KCCQ is a validated health related quality of life measure for heart failure. The KCCQ is a 23-item, self-administered instrument that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life. Clinical summary score is one of the quality of life variable of interest derived from KCCQ. Clinical summary score is the mean of domains: physical limitations score (6 items) and total symptom score (2 items [symptoms frequency and symptom burden]). The score is calculated by summing domain responses and then transforming scores to a 0-100 unit scale with higher scores indicating better health status. FAS included subjects which were randomized to double-blind study treatment. Here, 'N' (number of subjects analyzed) specifies all subjects who were evaluated for this endpoint.

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

End point timeframe:

Baseline to Week 24

| End point values | Placebo | Macitentan | | |
|--------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 71 | 69 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | 0.89 (\pm 17.72) | -2.37 (\pm 16.12) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis for Double-blind period |
| Comparison groups | Placebo v Macitentan |
| Number of subjects included in analysis | 140 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2172 |
| Method | ANCOVA |
| Parameter estimate | Least square mean |
| Point estimate | -3.5 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -8.17 |
| upper limit | 1.17 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.82 |

Secondary: Change from Baseline to Week 24 in Accelerometer-assessed Proportion of Time Spent in Light to Vigorous Physical Activity

| | |
|-----------------|---|
| End point title | Change from Baseline to Week 24 in Accelerometer-assessed Proportion of Time Spent in Light to Vigorous Physical Activity |
|-----------------|---|

End point description:

Physical activity is assessed by accelerometer as the proportion of time spent in light to vigorous physical activity based on a threshold of greater than (>)100 activity counts per minute and expressed as change from baseline to Week 24. FAS included subjects which were randomized to double-blind study treatment. Here, 'N' (number of participants analyzed) specifies all subjects who were evaluated for this endpoint.

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

End point timeframe:

Baseline to Week 24

| End point values | Placebo | Macitentan | | |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 31 | 30 | | |
| Units: proportion of time spent | | | | |
| arithmetic mean (standard deviation) | -0.005 (± 0.098) | -0.024 (± 0.084) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis for Double-blind period |
| Comparison groups | Placebo v Macitentan |
| Number of subjects included in analysis | 61 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3665 |
| Method | ANCOVA |
| Parameter estimate | Least square mean |
| Point estimate | -0.02 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -0.05 |
| upper limit | 0.02 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.02 |

Secondary: Number of Subjects with Worsening of Heart Failure (WHF) Events Over 52 Weeks

| | |
|-----------------|---|
| End point title | Number of Subjects with Worsening of Heart Failure (WHF) Events Over 52 Weeks |
|-----------------|---|

End point description:

Number of subjects with WHF events were reported. A WHF event includes HF death, hospitalization for WHF or an urgent visit for WHF. FAS included subjects which were randomized to double-blind study treatment.

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

End point timeframe:

Weeks 16, 24, 36, 52

| End point values | Placebo | Macitentan | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 71 | 71 | | |
| Units: subjects | | | | |
| Week 16 | 5 | 12 | | |
| Week 24 | 6 | 14 | | |
| Week 36 | 9 | 17 | | |
| Week 52 | 13 | 18 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 17 months

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

Dictionary used

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

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|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Macitentan |
|-----------------------|------------|

Reporting group description:

Subjects received macitentan 10 milligrams (mg) tablet orally once a day starting at Day 1 up to Week 52.

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

Reporting group description:

Subjects received placebo tablet orally once a day starting at Day 1 up to Week 52.

| Serious adverse events | Macitentan | Placebo | |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 29 / 71 (40.85%) | 23 / 71 (32.39%) | |
| number of deaths (all causes) | 2 | 5 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colon Cancer | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pancreatic Carcinoma | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Superficial Spreading Melanoma Stage Iv | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |

| | | | |
|--|----------------|----------------|--|
| Hypotension | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral Arterial Occlusive Disease | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral Ischaemia | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple Organ Dysfunction Syndrome | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Non-Cardiac Chest Pain | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema Peripheral | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Uterine Polyp | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute Pulmonary Oedema | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumopathy | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic Obstructive Pulmonary Disease | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural Effusion | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary Congestion | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Delirium | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mental Status Changes | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Investigations | | | |
| Ammonia Increased | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood Lactic Acid Increased | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoglobin Decreased | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic Enzyme Increased | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Ankle Fracture | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road Traffic Accident | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute Left Ventricular Failure | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina Pectoris | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 71 (1.41%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina Unstable | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial Fibrillation | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular Block Complete | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac Failure | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac Failure Acute | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac Failure Congestive | | | |
| subjects affected / exposed | 5 / 71 (7.04%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic Right Ventricular Failure | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left Ventricular Failure | | | |
| subjects affected / exposed | 3 / 71 (4.23%) | 2 / 71 (2.82%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Right Ventricular Failure | | | |
| subjects affected / exposed | 6 / 71 (8.45%) | 6 / 71 (8.45%) | |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Sinus Node Dysfunction | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebral Ischaemia | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular Accident | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic Stroke | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 2 / 71 (2.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 71 (1.41%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood Loss Anaemia | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Diabetic Retinopathy | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal Pain | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal Haemorrhage | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Congestive Hepatopathy | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash Pruritic | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute Kidney Injury | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 2 / 71 (2.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oliguria | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal Failure | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal Impairment | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back Pain | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle Twitching | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Gangrene | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 3 / 71 (4.23%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pyelonephritis Acute | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic Shock | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 2 / 71 (2.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Fluid Overload | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fluid Retention | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | Macitentan | Placebo | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 57 / 71 (80.28%) | 54 / 71 (76.06%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin Cancer | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 2 / 71 (2.82%) | |
| occurrences (all) | 0 | 2 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 2 / 71 (2.82%) | |
| occurrences (all) | 2 | 3 | |
| Hypotension | | | |
| subjects affected / exposed | 3 / 71 (4.23%) | 3 / 71 (4.23%) | |
| occurrences (all) | 3 | 3 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 3 / 71 (4.23%) | 1 / 71 (1.41%) | |
| occurrences (all) | 3 | 1 | |
| Fatigue | | | |
| subjects affected / exposed | 5 / 71 (7.04%) | 6 / 71 (8.45%) | |
| occurrences (all) | 5 | 6 | |
| Non-Cardiac Chest Pain | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 2 / 71 (2.82%) | |
| occurrences (all) | 1 | 2 | |
| Oedema Peripheral | | | |

| | | | |
|--|---|---|--|
| subjects affected / exposed occurrences (all) | 9 / 71 (12.68%) 13 | 4 / 71 (5.63%) 5 | |
| Reproductive system and breast disorders Gynaecomastia subjects affected / exposed occurrences (all) | 0 / 71 (0.00%) 0 | 2 / 71 (2.82%) 2 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Nasal Congestion subjects affected / exposed occurrences (all) Pleural Effusion subjects affected / exposed occurrences (all) | 2 / 71 (2.82%) 2 8 / 71 (11.27%) 9 2 / 71 (2.82%) 2 2 / 71 (2.82%) 2 | 4 / 71 (5.63%) 6 7 / 71 (9.86%) 10 1 / 71 (1.41%) 1 1 / 71 (1.41%) 1 | |
| Investigations Alanine Aminotransferase Increased subjects affected / exposed occurrences (all) Blood Creatinine Increased subjects affected / exposed occurrences (all) Blood Potassium Increased subjects affected / exposed occurrences (all) Blood Urea Increased subjects affected / exposed occurrences (all) Blood Uric Acid Increased subjects affected / exposed occurrences (all) Glomerular Filtration Rate Decreased | 2 / 71 (2.82%) 2 3 / 71 (4.23%) 3 1 / 71 (1.41%) 1 4 / 71 (5.63%) 4 1 / 71 (1.41%) 1 | 1 / 71 (1.41%) 1 2 / 71 (2.82%) 2 2 / 71 (2.82%) 2 1 / 71 (1.41%) 1 3 / 71 (4.23%) 3 | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 2 / 71 (2.82%) | 2 / 71 (2.82%) | |
| occurrences (all) | 2 | 2 | |
| Brain Natriuretic Peptide Increased | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 2 / 71 (2.82%) | |
| occurrences (all) | 0 | 2 | |
| Haemoglobin Decreased | | | |
| subjects affected / exposed | 3 / 71 (4.23%) | 3 / 71 (4.23%) | |
| occurrences (all) | 4 | 4 | |
| Weight Increased | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 3 / 71 (4.23%) | |
| occurrences (all) | 2 | 3 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 4 / 71 (5.63%) | |
| occurrences (all) | 1 | 4 | |
| Cardiac disorders | | | |
| Atrial Fibrillation | | | |
| subjects affected / exposed | 4 / 71 (5.63%) | 5 / 71 (7.04%) | |
| occurrences (all) | 4 | 5 | |
| Angina Pectoris | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 0 / 71 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Atrial Flutter | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 1 / 71 (1.41%) | |
| occurrences (all) | 2 | 1 | |
| Cardiac Failure Congestive | | | |
| subjects affected / exposed | 3 / 71 (4.23%) | 1 / 71 (1.41%) | |
| occurrences (all) | 3 | 1 | |
| Left Ventricular Failure | | | |
| subjects affected / exposed | 5 / 71 (7.04%) | 0 / 71 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 2 / 71 (2.82%) | |
| occurrences (all) | 0 | 2 | |
| Right Ventricular Failure | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 5 / 71 (7.04%) 6 | 2 / 71 (2.82%) 2 | |
| Nervous system disorders | | | |
| Cerebral Ischaemia | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 0 / 71 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Dizziness | | | |
| subjects affected / exposed | 3 / 71 (4.23%) | 3 / 71 (4.23%) | |
| occurrences (all) | 3 | 3 | |
| Headache | | | |
| subjects affected / exposed | 4 / 71 (5.63%) | 1 / 71 (1.41%) | |
| occurrences (all) | 4 | 1 | |
| Lethargy | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 1 / 71 (1.41%) | |
| occurrences (all) | 2 | 1 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 2 / 71 (2.82%) | |
| occurrences (all) | 1 | 2 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 5 / 71 (7.04%) | 3 / 71 (4.23%) | |
| occurrences (all) | 6 | 3 | |
| Blood Loss Anaemia | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 1 / 71 (1.41%) | |
| occurrences (all) | 2 | 1 | |
| Hypochromic Anaemia | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 0 / 71 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Iron Deficiency Anaemia | | | |
| subjects affected / exposed | 4 / 71 (5.63%) | 1 / 71 (1.41%) | |
| occurrences (all) | 4 | 1 | |
| Normocytic Anaemia | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 1 / 71 (1.41%) | |
| occurrences (all) | 2 | 1 | |
| Gastrointestinal disorders | | | |

| | | | |
|--|---------------------|---------------------|--|
| Abdominal Pain Upper subjects affected / exposed occurrences (all) | 2 / 71 (2.82%) 2 | 0 / 71 (0.00%) 0 | |
| Ascites subjects affected / exposed occurrences (all) | 2 / 71 (2.82%) 2 | 1 / 71 (1.41%) 1 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 2 / 71 (2.82%) 3 | 2 / 71 (2.82%) 3 | |
| Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all) | 2 / 71 (2.82%) 2 | 0 / 71 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) | 3 / 71 (4.23%) 3 | 0 / 71 (0.00%) 0 | |
| Renal and urinary disorders Acute Kidney Injury subjects affected / exposed occurrences (all) | 5 / 71 (7.04%) 5 | 2 / 71 (2.82%) 3 | |
| Renal Failure subjects affected / exposed occurrences (all) | 2 / 71 (2.82%) 2 | 4 / 71 (5.63%) 4 | |
| Renal Impairment subjects affected / exposed occurrences (all) | 5 / 71 (7.04%) 5 | 1 / 71 (1.41%) 1 | |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 1 / 71 (1.41%) 1 | 2 / 71 (2.82%) 2 | |
| Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all) | 2 / 71 (2.82%) 2 | 3 / 71 (4.23%) 3 | |
| Muscle Spasms | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 4 / 71 (5.63%) | 1 / 71 (1.41%) | |
| occurrences (all) | 4 | 2 | |
| Pain in Extremity | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 4 / 71 (5.63%) | |
| occurrences (all) | 1 | 5 | |
| Neck Pain | | | |
| subjects affected / exposed | 0 / 71 (0.00%) | 3 / 71 (4.23%) | |
| occurrences (all) | 0 | 3 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 4 / 71 (5.63%) | 2 / 71 (2.82%) | |
| occurrences (all) | 4 | 2 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 0 / 71 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Lower Respiratory Tract Infection | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 0 / 71 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 4 / 71 (5.63%) | 1 / 71 (1.41%) | |
| occurrences (all) | 4 | 1 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 5 / 71 (7.04%) | |
| occurrences (all) | 2 | 5 | |
| Respiratory Tract Infection Viral | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 2 / 71 (2.82%) | |
| occurrences (all) | 3 | 2 | |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 4 / 71 (5.63%) | |
| occurrences (all) | 2 | 5 | |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 5 / 71 (7.04%) | |
| occurrences (all) | 2 | 8 | |
| Viral Upper Respiratory Tract Infection | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 71 (2.82%) 2 | 0 / 71 (0.00%) 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 2 / 71 (2.82%) | |
| occurrences (all) | 1 | 2 | |
| Fluid Retention | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 1 / 71 (1.41%) | |
| occurrences (all) | 2 | 1 | |
| Gout | | | |
| subjects affected / exposed | 6 / 71 (8.45%) | 2 / 71 (2.82%) | |
| occurrences (all) | 6 | 2 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 3 / 71 (4.23%) | 4 / 71 (5.63%) | |
| occurrences (all) | 4 | 4 | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 2 / 71 (2.82%) | |
| occurrences (all) | 2 | 2 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 3 / 71 (4.23%) | 3 / 71 (4.23%) | |
| occurrences (all) | 3 | 3 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 71 (1.41%) | 2 / 71 (2.82%) | |
| occurrences (all) | 2 | 2 | |
| Iron Deficiency | | | |
| subjects affected / exposed | 2 / 71 (2.82%) | 0 / 71 (0.00%) | |
| occurrences (all) | 2 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 08 February 2017 | The overall reason for the amendment 1 was implementation of additional safety monitoring measures after first dose of macitentan, as requested by the Food and Drug Administration (FDA). |
| 12 April 2017 | The overall reason for the amendment 2 was addition of medications mainly transported by breast-cancer resistant protein to the list of forbidden medications, as requested by the FDA. |
| 10 April 2018 | The overall reason for the amendment 3 was added description of transition to the SERENADE Open-label (OL) extension study, revision of the eligibility and run-in failure criteria, and introduction of a Clinical Event Committee (CEC). Changes made to the statistical methods to allow N-terminal pro-brain natriuretic peptide values measured at screening to be used for stratification at time of treatment assignment and to the definitions of the placebo run-in and macitentan analysis sets. |
| 08 March 2019 | The overall reason for the amendment 4 was Addition of the 6-minute walk distance (6MWD) substudy to assess the change in exercise capacity from baseline and removal of the 8-hour safety monitoring period after first dose of macitentan at the start of macitentan run-in. Addition of 2 telephone calls to ensure adequate safety follow-up is established during the run-in phase. Reordered testing hierarchy of the key secondary efficacy endpoints: Kansas City Cardiomyopathy Questionnaire was moved to the first secondary endpoint and accelerometry moved to the second position. Added new hierarchical composite exploratory efficacy endpoint which combined hard (death, hospitalizations) and soft (functional capacity, quality of life) endpoints to allow for a more complete and broader assessment of clinical benefit. |
| 06 February 2020 | Overall reason for amendment 5 was early termination of enrollment. Subject recruitment targets not met and completion of study within reasonable timeline not realistic. Updated sample size to reflect early termination of recruitment. Reduced length of double-blind treatment (DBT) period to 24 weeks. Week 24 was pre-defined timepoint to assess primary as well as key secondary endpoints. Secondary endpoint of time to worsening HF event however was planned to be assessed up to Week 52 to gather meaningful information for preparation of pivotal clinical trial development program. Due to reduced sample size, number of worsening HF events was expected to be too low for meaningful analysis of time to worsening HF. DBT period was to be stopped at Week 24, and eligible subjects were to be transitioned to SERENADE OL at that timepoint. Subjects who completed Week 24 visit, were scheduled to come back for an EoT visit within 60 days and enroll in OL study, if eligible. Not all sites participated in OL study. Removed CEC which was appointed to review and adjudicate in blinded fashion worsening HF events, reasons for hospitalization, and causes of death, did not affect safety monitoring and therefore decision was also endorsed by IDMC. DBT period reduced from 52 to 24 weeks, low occurrence of worsening HF events which would not allow for meaningful conclusions to be drawn. Investigator assessment of worsening HF events continued. Re-scheduled accelerometry to be performed 9 consecutive days prior to Week 24 for subjects completing Week 24 to ensure assessment performed on DBT. Stopped sub study assessments (6MWD and Borg Dyspnea Index), due to low count of subjects participating in sub study to allow for meaningful interpretation of results. Planned analysis of sub study data amended to reflect above amendment to protocol. Removed new hierarchical composite exploratory efficacy endpoint that was added in prior amendment due to reduced sample size and stopping of 6MWT sub study. |

| | |
|--------------|---|
| 16 July 2020 | Overall reason for amendment 6 was updated the concomitant therapy sections pertaining to new information regarding a drug-drug-interaction of macitentan with moderate dual cytochrome P450 (CYP)3A4 and CYP2C9 inhibitors or co-administration of a combination of moderate CYP3A4 inhibitors and moderate CYP2C9 inhibitors. Data from clinical trials with macitentan 10 mg were reviewed, identifying cases where macitentan 10 mg was administered concomitantly with dual CYP3A4/CYP2C9 inhibitors, such as fluconazole and amiodarone. The review indicated that co-administration of fluconazole or amiodarone with macitentan was not common (between 1% to 3% of subjects). No safety concerns were identified with concurrent administration of fluconazole or amiodarone and macitentan 10 mg. |
|--------------|---|

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.

Recruitment was stopped prematurely in December 2019 due to slow enrollment which resulted in an underpowered study and impacted the meaningful interpretation of the results.

Notes: