# Clinical trial results:
# A multi-center, double-blind, randomized, placebo-controlled, parallel-group, Phase 3 study to evaluate the effects of macitentan on exercise capacity in subjects with Eisenmenger Syndrome

## Summary

| | |
|---|---|
| EudraCT number | 2012-003335-33 |
| Trial protocol | GB IT BG BE DE PT NL AT ES HU CZ GR |
| Global end of trial date | 01 December 2016 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 24 June 2017 |
| First version publication date | 24 June 2017 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | AC-055-305 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01743001 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Actelion Pharmaceuticals Ltd |
| Sponsor organisation address | Gewerbestr. 16, Allschwil, Switzerland, 4123 |
| Public contact | Actelion Pharmaceuticals Ltd, clinical trial disclosure desk, clinical-trials-disclosure@actelion.com |
| Scientific contact | Actelion Pharmaceuticals Ltd, clinical trial disclosure desk, clinical-trials-disclosure@actelion.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? | Yes |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 10 January 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 December 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 December 2016 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the effects of macitentan on exercise capacity in subjects with Eisenmenger Syndrome

Protection of trial subjects:

Prior to the start of the study, each study site consulted an Independent Ethics Committee (IEC) or Institutional Review Board (IRB), i.e., a review panel that was responsible for ensuring the protection of the rights, safety and well-being of human subjects involved in a clinical investigation.
The study was conducted in compliance with the principles of the 'Declaration of Helsinki', the International Council for Harmonisation (ICH)-Good Clinical Practice (GCP) guidelines, and with the laws and regulations of the country in which the clinical research was conducted.
Both Actelion and the investigator had the right to terminate the study at any time, and in such a case, were responsible for protecting the subjects' interests.
Prior to any study procedure and after adequate explanation of the aims, methods, objectives, and potential hazards of the study, written informed consent was obtained from each participating adult subject (including DS subjects who were able to consent), as well as from the parent(s) or legal representative(s) of each participating minor, and from the parent(s)/legal representative(s) or caregiver(s) of each participating subject with DS, who was not able to personally read and sign the informed consent. Additionally, written assent was obtained from each minor and each DS subject who was unable to give written consent. All subjects who participated in the hemodynamic sub-study were required to sign a separate informed consent form (ICF). Informed consent/assent was obtained in accordance with the national laws or regulations.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 21 May 2013 |
| 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 | China: 70 |
| Country: Number of subjects enrolled | Malaysia: 3 |
| Country: Number of subjects enrolled | Philippines: 2 |
| Country: Number of subjects enrolled | Vietnam: 16 |
| Country: Number of subjects enrolled | Bulgaria: 6 |
| Country: Number of subjects enrolled | Poland: 10 |
| Country: Number of subjects enrolled | Romania: 8 |
| Country: Number of subjects enrolled | Russian Federation: 19 |
| Country: Number of subjects enrolled | Serbia: 9 |
| Country: Number of subjects enrolled | Chile: 7 |
| Country: Number of subjects enrolled | Mexico: 30 |

| | |
|---|---|
| Country: Number of subjects enrolled | United States: 7 |
| Country: Number of subjects enrolled | Austria: 3 |
| Country: Number of subjects enrolled | France: 17 |
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | Greece: 3 |
| Country: Number of subjects enrolled | Israel: 1 |
| Country: Number of subjects enrolled | Portugal: 7 |
| Country: Number of subjects enrolled | Spain: 3 |
| Country: Number of subjects enrolled | Turkey: 1 |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Worldwide total number of subjects | 226 |
| EEA total number of subjects | 61 |

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) | 15 |
| Adults (18-64 years) | 211 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

71 sites in 26 countries

### Pre-assignment

Screening details:

The screening period lasted a maximum of 30 days from Visit 1 up to Randomization (Visit 2). Total of 319 screened subjects.

### Period 1

| | |
|---|---|
| Period 1 title | Baseline period |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Macitentan |

Arm description:

Macitentan

| | |
|---|---|
| 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, once-daily, oral, film-coated tablet

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

Placebo

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

Dosage and administration details:

Placebo, once-daily, oral, film-coated tablet

| Number of subjects in period 1 | Macitentan | Placebo |
|---|---|---|
| Started | 114 | 112 |
| Completed | 114 | 112 |

| Period 2 | |
|---|---|
| Period 2 title | Overall Study |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

| Arms | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Macitentan |

Arm description:

Subjects receive macitentan 10 mg oral tablet once daily

| | |
|---|---|
| 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, once-daily, oral, film-coated tablet

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

Subjects receive macitentan-matching placebo oral tablet once daily

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

Dosage and administration details:

Placebo, once-daily, oral, film-coated tablet

| **Number of subjects in period 2** | Macitentan | Placebo |
|---|---|---|
| Started | 114 | 112 |
| Completed | 111 | 112 |
| Not completed | 3 | 0 |
| Adverse event, serious fatal | 1 | - |
| Physician decision | 1 | - |
| Pregnancy | 1 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Macitentan |
| Reporting group description: Macitentan | |
| Reporting group title | Placebo |
| Reporting group description: Placebo | |

| Reporting group values | Macitentan | Placebo | Total |
|---|---|---|---|
| Number of subjects | 114 | 112 | 226 |
| Age categorical | | | |
| Full analysis set (FAS) | | | |
| Units: Subjects | | | |
| Adolescents (12-17 years) | 13 | 2 | 15 |
| Adults (18 - 55 years) | 90 | 105 | 195 |
| Adults >= 55 years | 11 | 5 | 16 |
| Age continuous | | | |
| Full analysis set (FAS) | | | |
| Units: years | | | |
| median | 33 | 31 | |
| full range (min-max) | 12 to 82 | 13 to 62 | - |
| Gender categorical<br><br>Units: Subjects | | | |
| Female | 82 | 68 | 150 |
| Male | 32 | 44 | 76 |

| Subject analysis sets | |
|---|---|
| Subject analysis set title | Full analysis set (FAS) |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The full analysis set (FAS) included all subjects from the SCR allocated to a randomized study treatment. Subjects were evaluated according to the study treatment to which they were assigned. All available data were taken into account for the analysis.

| | |
|---|---|
| Subject analysis set title | Per-protocol analysis set (PPS) |
| Subject analysis set type | Per protocol |

Subject analysis set description:

The per-protocol analysis set (PPS) comprised data from all subjects included in the FAS without major protocol deviations or conditions, which might have affected the evaluation of the effect of the study treatment on the primary efficacy endpoint.

| Reporting group values | Full analysis set (FAS) | Per-protocol analysis set (PPS) | |
|---|---|---|---|
| Number of subjects | 226 | 200 | |
| Age categorical | | | |
| Full analysis set (FAS) | | | |
| Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Adolescents (12-17 years) | 15 | 13 | |
| Adults (18 - 55 years) | 195 | 176 | |
| Adults >= 55 years | 16 | 11 | |
| Age continuous | | | |
| Full analysis set (FAS) | | | |
| Units: years | | | |
| median | 32 | 32 | |
| full range (min-max) | 12 to 82 | 12 to 82 | |
| Gender categorical<br><br>Units: Subjects | | | |
| Female | 150 | 132 | |
| Male | 76 | 68 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Macitentan |
| Reporting group description: | |
| Macitentan | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo | |
| Reporting group title | Macitentan |
| Reporting group description: | |
| Subjects receive macitentan 10 mg oral tablet once daily | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects receive macitentan-matching placebo oral tablet once daily | |
| Subject analysis set title | Full analysis set (FAS) |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The full analysis set (FAS) included all subjects from the SCR allocated to a randomized study treatment. Subjects were evaluated according to the study treatment to which they were assigned. All available data were taken into account for the analysis.

| | |
|---|---|
| Subject analysis set title | Per-protocol analysis set (PPS) |
| Subject analysis set type | Per protocol |

Subject analysis set description:

The per-protocol analysis set (PPS) comprised data from all subjects included in the FAS without major protocol deviations or conditions, which might have affected the evaluation of the effect of the study treatment on the primary efficacy endpoint.

### Primary: Change from baseline to Week 16 in exercise capacity, as measured by 6MWD

| | |
|---|---|
| End point title | Change from baseline to Week 16 in exercise capacity, as measured by 6MWD |

End point description:

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

End point timeframe:

From baseline to Week 16

| End point values | Macitentan | Placebo | Full analysis set (FAS) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 114 | 112 | 0[1] | |
| Units: meter | | | | |
| arithmetic mean (standard deviation) | 18.3 (± 84.4) | 19.7 (± 53) | () | |

Notes:

[1] - NA

## Statistical analyses

| Statistical analysis title | Main analysis |
|---|---|

Statistical analysis description:

ANCOVA for the change from baseline to Week 16 including randomized treatment group, presence of DS (yes/no), WHO FC (II vs III/IV) and baseline 6MWD value as covariates

| | |
|---|---|
| Comparison groups | Macitentan v Placebo |
| Number of subjects included in analysis | 226 |
| Analysis specification | Pre-specified |
| Analysis type | other[2] |
| P-value | = 0.612 |
| Method | ANCOVA |
| Parameter estimate | Least-square mean difference |
| Point estimate | -4.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.8 |
| upper limit | 13.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 9.2 |

Notes:

[2] - ANCOVA

## Secondary: Change from baseline to Week 16 in WHO functional class

| End point title | Change from baseline to Week 16 in WHO functional class |
|---|---|

End point description:

WHO functional class dichotomized as improvement from baseline to Week 16 'Yes' (i.e., shift to lower class [e.g., from III to II]) or 'No' (i.e., shift to higher class [e.g., from III to IV] or unchanged).

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

End point timeframe:

From baseline to Week 16

| End point values | Macitentan | Placebo | Full analysis set (FAS) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 114 | 112 | 0[3] | |
| Units: Participants | 10 | 16 | | |

Notes:

[3] - NA

### Statistical analyses

| Statistical analysis title | Main analysis |
|---|---|

Statistical analysis description:

Logistic regression model for the improvement from baseline to Week 16 including randomized treatment group and location of cardiac defect (pre-tricuspid/ post-tricuspid) as categorical factors

| | |
|---|---|
| Comparison groups | Macitentan v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 226 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.145 |
| Method | Wlad chi-square test |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.23 |
| upper limit | 1.24 |

## Secondary: Change from baseline to Week 16 in dyspnea (assessed by the Borg dyspnea index)

| | |
|---|---|
| End point title | Change from baseline to Week 16 in dyspnea (assessed by the Borg dyspnea index) |

End point description:

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

End point timeframe:

From baseline to Week 16

| End point values | Macitentan | Placebo | Full analysis set (FAS) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 114 | 112 | 0[4] | |
| Units: Index | | | | |
| arithmetic mean (standard deviation) | | | | |
| Index | -0.22 (± 1.56) | -0.29 (± 1.5) | () | |

Notes:

[4] - NA

### Statistical analyses

| Statistical analysis title | Main analysis |
|---|---|

Statistical analysis description:

ANCOVA for the change from baseline to Week 16 including randomized treatment group and location of cardiac defect (pre-tricuspid/ post-tricuspid) and baseline Borg dyspnea index as covariates

| | |
|---|---|
| Comparison groups | Macitentan v Placebo |
| Number of subjects included in analysis | 226 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.8456 [5] |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Macitentan - Placebo |
| Point estimate | 0.06 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.34 |
| upper limit | 0.46 |

Notes:

[5] - P-value Wilcoxon rank sum test

## Secondary: Change from baseline to Week 16 in quality of life (assessed by the SF-36 questionnaire)

| End point title | Change from baseline to Week 16 in quality of life (assessed by the SF-36 questionnaire) |
|---|---|

End point description:

SF-36 PHYSICAL FUNCTIONING, SF-36 ROLE-PHYSICAL, SF-36 PAIN INDEX, SF-36 GENERAL HEALTH PERCEPTIONS, SF-36 VITALITY, SF-36 SOCIAL FUNCTIONING, SF-36 ROLE-EMOTIONAL, and SF-36 MENTAL HEALTH INDEX

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

End point timeframe:

From baseline to Week 16

| **End point values** | Macitentan | Placebo | Full analysis set (FAS) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 101 | 99 | 0[6] | |
| Units: Scores | | | | |
| least squares mean (standard error) | | | | |
| SF-36 PHYSICAL FUNCTIONING | 4.4 (± 1.5) | 5.3 (± 1.6) | () | |
| SF-36 ROLE-PHYSICAL | 5.7 (± 2) | 7.2 (± 2.1) | () | |
| SF-36 PAIN INDEX | 3.2 (± 2.3) | 3.1 (± 2.4) | () | |
| SF-36 GENERAL HEALTH PERCEPTIONS | 5 (± 1.6) | 1.9 (± 1.7) | () | |
| SF-36 VITALITY | 6.9 (± 1.6) | 5.8 (± 1.7) | () | |
| SF-36 SOCIAL FUNCTIONING | 1.3 (± 2.2) | 2.6 (± 2.3) | () | |
| SF-36 ROLE-EMOTIONAL | 1.7 (± 2.2) | 4.6 (± 2.4) | () | |
| SF-36 MENTAL HEALTH INDEX | 2.8 (± 1.5) | 5.1 (± 1.6) | () | |

Notes:

[6] - NA

### Statistical analyses

| **Statistical analysis title** | SF-36 PHYSICAL FUNCTIONING |
|---|---|
| Comparison groups | Macitentan v Placebo |
| Number of subjects included in analysis | 200 |
| Analysis specification | Pre-specified |
| Analysis type | other[7] |
| Method | ANCOVA |
| Parameter estimate | Macitentan - Placebo |
| Point estimate | -1 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5 |
| upper limit | 3.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.1 |

Notes:

[7] - Statistical model is an ANCOVA (analysis of covariance) adjusting for randomized treatment group and location of cardiac defect (as factors), and baseline score (as covariate).

| **Statistical analysis title** | SF-36 ROLE-PHYSICAL |
|---|---|

Statistical analysis description:

Statistical model is an ANCOVA (analysis of covariance) adjusting for randomized treatment group and location of cardiac defect (as factors), and baseline score (as covariate).

| | |
|---|---|
| Comparison groups | Macitentan v Placebo |
| Number of subjects included in analysis | 200 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Method | ANCOVA |
| Parameter estimate | Macitentan - Placebo |
| Point estimate | -1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.7 |
| upper limit | 3.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.7 |

| **Statistical analysis title** | SF-36 PAIN INDEX |
|---|---|

Statistical analysis description:

Statistical model is an ANCOVA (analysis of covariance) adjusting for randomized treatment group and location of cardiac defect (as factors), and baseline score (as covariate).

| | |
|---|---|
| Comparison groups | Macitentan v Placebo |
| Number of subjects included in analysis | 200 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Method | ANCOVA |
| Parameter estimate | Macitentan - Placebo |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.9 |
| upper limit | 6.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.1 |

| **Statistical analysis title** | SF-36 GENERAL HEALTH PERCEPTIONS |
|---|---|
| Statistical analysis description: | |
| Statistical model is an ANCOVA (analysis of covariance) adjusting for randomized treatment group and location of cardiac defect (as factors), and baseline score (as covariate). | |
| Comparison groups | Macitentan v Placebo |
| Number of subjects included in analysis | 200 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Method | ANCOVA |
| Parameter estimate | Macitentan - Placebo |
| Point estimate | 3.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.2 |
| upper limit | 7.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.2 |

| **Statistical analysis title** | SF-36 VITALITY |
|---|---|
| Statistical analysis description: | |
| Statistical model is an ANCOVA (analysis of covariance) adjusting for randomized treatment group and location of cardiac defect (as factors), and baseline score (as covariate). | |
| Comparison groups | Macitentan v Placebo |
| Number of subjects included in analysis | 200 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Macitentan - Placebo |
| Point estimate | 1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.1 |
| upper limit | 5.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.1 |

| **Statistical analysis title** | SF-36 SOCIAL FUNCTIONING |
|---|---|
| Statistical analysis description: | |
| Statistical model is an ANCOVA (analysis of covariance) adjusting for randomized treatment group and location of cardiac defect (as factors), and baseline score (as covariate). | |
| Comparison groups | Macitentan v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 200 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Macitentan - Placebo |
| Point estimate | -1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.2 |
| upper limit | 4.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.9 |

| **Statistical analysis title** | SF-36 ROLE-EMOTIONAL |
|---|---|
| Statistical analysis description: | |
| Statistical model is an ANCOVA (analysis of covariance) adjusting for randomized treatment group and location of cardiac defect (as factors), and baseline score (as covariate). | |
| Comparison groups | Macitentan v Placebo |
| Number of subjects included in analysis | 200 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Macitentan - Placebo |
| Point estimate | -2.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.7 |
| upper limit | 3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3 |

| **Statistical analysis title** | SF-36 MENTAL HEALTH INDEX |
|---|---|
| Statistical analysis description: | |
| Statistical model is an ANCOVA (analysis of covariance) adjusting for randomized treatment group and location of cardiac defect (as factors), and baseline score (as covariate). | |
| Comparison groups | Macitentan v Placebo |
| Number of subjects included in analysis | 200 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Macitentan - Placebo |
| Point estimate | -2.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.4 |
| upper limit | 1.8 |

| Variability estimate | Standard error of the mean |
|---|---|
| Dispersion value | 2.1 |

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| From study treatment initiation up to 30 days after study treatment discontinuation | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19 |

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| 112 subjects were exposed to Placebo for 15.96 weeks on average | |
| Reporting group title | Macitentan_10_mg |
| Reporting group description: | |
| 114 subjects were exposed to Macitentan 10mg for 15.93 weeks on average | |

| Serious adverse events | Placebo | Macitentan_10_mg | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 112 (1.79%) | 7 / 114 (6.14%) | |
| number of deaths (all causes) | 0 | 1 | |
| number of deaths resulting from adverse events | | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 112 (0.89%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 1 / 112 (0.89%) | 0 / 114 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Right ventricular failure | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 3 / 114 (2.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Dizziness | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Endocarditis | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 2 / 114 (1.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Placebo | Macitentan_10_mg | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 30 / 112 (26.79%) | 31 / 114 (27.19%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 5 / 112 (4.46%) | 13 / 114 (11.40%) | |
| occurrences (all) | 5 | 15 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Haemoptysis | | | |
| subjects affected / exposed | 6 / 112 (5.36%) | 0 / 114 (0.00%) | |
| occurrences (all) | 8 | 0 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 3 / 112 (2.68%) | 6 / 114 (5.26%) | |
| occurrences (all) | 3 | 6 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 14 / 112 (12.50%) | 3 / 114 (2.63%) | |
| occurrences (all) | 16 | 4 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 7 / 112 (6.25%) | 11 / 114 (9.65%) | |
| occurrences (all) | 10 | 12 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 03 April 2013 | Amendment 1 - Changes included:<br>- Efficacy as well as safety and tolerability endpoints sections were revised;<br>- The main efficacy analysis plan was updated<br>- The alternative analysis methods described initially for the main analysis, in case assumptions of normality and homogeneity of variance are not met following an assessment, were changed to a sensitivity analysis.<br>- The overall study design and plan were modified to allow those subjects who did not meet the eligibility criteria for the sub-study to be considered for the main study on a case-by-case basis.<br>- Exclusion criterion 5 concerning systolic blood pressure was updated<br>- Other changes. |
| 13 March 2014 | Global Amendment 2 - Changes included:<br>- The study design and eligibility criteria were modified to allow the participation of additional subjects with more complex cardiac defects, including those with Down Syndrom,<br>- Inclusion criterion 3 was revised;<br>- Cardiac catheterization requirements (inclusion criterion 4) were updated;<br>- The limit of variance between the 2 6MWT at screening was increased to 15% (inclusion criterion 6).<br>- Exclusion criterion 1 was revised to rule out (1) other causes of pulmonary hypertension<br>- Other changes. |

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.

There were no significant limitations of the trial.

Notes: