# Clinical trial results:
# Prospective, randomized, placebo-controlled, double-blind, multicenter, parallel-group, 24-week study to assess the efficacy, safety and tolerability of macitentan in subjects with inoperable chronic thromboembolic pulmonary hypertension

## Summary

| | |
|---|---|
| EudraCT number | 2013-002950-56 |
| Trial protocol | CZ DE AT BE GB HU NL LT |
| Global end of trial date | 28 September 2016 |

### Results information

| | |
|---|---|
| Result version number | v3 (current) |
| This version publication date | 11 June 2020 |
| First version publication date | 18 October 2017 |
| Version creation reason | • New data added to full data set<br>FDS updated per CSR Addendum-2. |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | AC-055E201 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02021292 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Actelion Pharmaceuticals Ltd. |
| Sponsor organisation address | Gewerbestrasse 16, Allschwil, Switzerland, 4123 |
| Public contact | Clinical Trial Disclosure Desk, Actelion Pharmaceuticals Ltd., clinical-trials-disclosure@actelion.com |
| Scientific contact | Clinical Trial Disclosure Desk, Actelion Pharmaceuticals Ltd., 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? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 25 October 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 September 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 September 2016 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the effect of macitentan 10 mg on pulmonary vascular resistance (PVR) at rest in comparison with placebo in subjects with inoperable chronic thromboembolic pulmonary hypertension (CTEPH).

Protection of trial subjects:

Prior to the start of the trial the study center consulted an Independent Ethics Committee (IEC), i.e., a review panel that was responsible for ensuring the protection of the rights, safety, and well-being of human patients involved in a clinical investigation. The sponsor ensured that the IEC consulted was adequately constituted to provide assurance of that protection, and maintained a list of committee members and their qualifications. The protocol and any material provided to the patient (such as a subject information sheet or description of the study used to obtain informed consent) were reviewed and approved by the appropriate IEC before the study was started. This study was conducted in full conformance with the principles of the 'Declaration of Helsinki' and with the laws and regulations of the country in which the 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 patients' interests. Written informed consent was obtained from each individual participating in the study prior to any study procedure and after adequate explanation of the aims, methods, objectives, and potential hazards of the study. It was made clear to each patient that he or she was completely free to refuse to enter the study, or to withdraw from it at any time for any reason. A description of any incentives to participate in the study was provided in the informed consent form.

Background therapy:

49 of 80 randomized subjects (61.3%) received PAH-specific background therapy at baseline (24 or 60% of subjects on macitentan and 25 or 62.5% of subjects on placebo).

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 20 August 2014 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy, Safety |
| Long term follow-up duration | 4 Years |
| 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: 24 |
| Country: Number of subjects enrolled | Czech Republic: 2 |
| Country: Number of subjects enrolled | France: 3 |
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | Hungary: 4 |
| Country: Number of subjects enrolled | Korea, Republic of: 1 |

| | |
|---|---|
| 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: 21 |
| Country: Number of subjects enrolled | Switzerland: 1 |
| Country: Number of subjects enrolled | Thailand: 4 |
| Country: Number of subjects enrolled | Turkey: 2 |
| Country: Number of subjects enrolled | Ukraine: 4 |
| Country: Number of subjects enrolled | United Kingdom: 3 |
| Worldwide total number of subjects | 80 |
| EEA total number of subjects | 21 |

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) | 52 |
| From 65 to 84 years | 28 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

A total of 48 sites in 20 countries screened subjects for recruitment. The study was conducted (i.e., randomized subjects) in a total of 36 sites across 16 countries: Belgium, China, Czech Republic, France, Germany, Hungary, Lithuania, Mexico, Poland, Russia, Thailand, Turkey, South Korea, Switzerland, Ukraine, and the United Kingdom.

### Pre-assignment

Screening details:

The target screening period from Visit 1 up to Randomization was a maximum of 30 days, but a longer period (up to 60 days) was permitted with pre-approval from Actelion. A total of 186 subjects were screened.

### Period 1

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

### Arms

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

Arm description:

Macitentan 10 mg, oral tablet, to be taken once daily.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Macitentan |
| Investigational medicinal product code | ACT-064992 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

10 mg tablet, once daily

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

Arm description:

Matching placebo oral tablet, to be taken 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

| **Number of subjects in period 1** | Macitentan | Placebo |
|---|---|---|
| Started | 40 | 40 |
| Completed | 40 | 37 |
| Not completed | 0 | 3 |
| Physician decision | - | 1 |
| Death | - | 1 |
| Lost to follow-up | - | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Macitentan |
| Reporting group description: | |
| Macitentan 10 mg, oral tablet, to be taken once daily. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Matching placebo oral tablet, to be taken once daily. | |

| Reporting group values | Macitentan | Placebo | Total |
|---|---|---|---|
| Number of subjects | 40 | 40 | 80 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age 18-64 years | 26 | 26 | 52 |
| Age 65-84 years | 14 | 14 | 28 |
| Age continuous | | | |
| Units: years | | | |
| median | 60.0 | 58.0 | |
| full range (min-max) | 20 to 80 | 23 to 78 | - |
| Gender categorical | | | |
| Units: | | | |
| Female | 26 | 25 | 51 |
| Male | 14 | 15 | 29 |
| Region of enrollment | | | |
| Units: Subjects | | | |
| Asia | 15 | 14 | 29 |
| Eastern Europe | 17 | 19 | 36 |
| Latin America | 1 | 1 | 2 |
| Western Europe | 7 | 6 | 13 |
| WHO functional class | | | |
| Units: Subjects | | | |
| class II | 12 | 6 | 18 |
| class III | 28 | 33 | 61 |
| class IV | 0 | 1 | 1 |
| Body Mass Index (BMI) | | | |
| Units: kg/m2 | | | |
| median | 25.7 | 26.0 | |
| full range (min-max) | 19.8 to 47.5 | 18.3 to 36.2 | - |
| 6-minute walk distance (6MWD) | | | |
| Units: meter | | | |
| arithmetic mean | 353.0 | 351.2 | |
| standard deviation | ± 87.90 | ± 73.79 | - |
| Pulmonary vascular resistance (PVR) | | | |
| Units: dyn.sec/cm5 | | | |
| arithmetic mean | 929.2 | 984.3 | |
| standard deviation | ± 379.65 | ± 487.06 | - |
| Time since diagnosis of chronic thromboembolic pulmonary | | | |

| | | | |
|---|---|---|---|
| hypertension (CTEPH) | | | |
| Units: years | | | |
| arithmetic mean | 1.7 | 1.2 | |
| standard deviation | ± 2.36 | ± 1.95 | - |

## 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 assigned to a study treatment. In order to adhere to the intention-to-treat principle as much as possible: 1) subjects were evaluated according to the study treatment they have been assigned to; and 2) all available data were included.

| **Reporting group values** | Full analysis set (FAS) | | |
|---|---|---|---|
| Number of subjects | 80 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Age 18-64 years | 52 | | |
| Age 65-84 years | 28 | | |
| Age continuous | | | |
| Units: years | | | |
| median | 59.0 | | |
| full range (min-max) | 20 to 80 | | |
| Gender categorical | | | |
| Units: | | | |
| Female | 51 | | |
| Male | 29 | | |
| Region of enrollment | | | |
| Units: Subjects | | | |
| Asia | 29 | | |
| Eastern Europe | 36 | | |
| Latin America | 2 | | |
| Western Europe | 13 | | |
| WHO functional class | | | |
| Units: Subjects | | | |
| class II | 18 | | |
| class III | 61 | | |
| class IV | 1 | | |
| Body Mass Index (BMI) | | | |
| Units: kg/m2 | | | |
| median | 25.7 | | |
| full range (min-max) | 18.3 to 47.5 | | |
| 6-minute walk distance (6MWD) | | | |
| Units: meter | | | |
| arithmetic mean | 352.1 | | |
| standard deviation | ± 80.64 | | |
| Pulmonary vascular resistance (PVR) | | | |
| Units: dyn.sec/cm5 | | | |
| arithmetic mean | 956.8 | | |
| standard deviation | ± 434.78 | | |

| | | | |
|---|---|---|---|
| Time since diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) | | | |
| Units: years | | | |
| arithmetic mean | 1.5 | | |
| standard deviation | ± 2.16 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Macitentan |
| Reporting group description: | |
| Macitentan 10 mg, oral tablet, to be taken once daily. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Matching placebo oral tablet, to be taken 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 assigned to a study treatment. In order to adhere to the intention-to-treat principle as much as possible: 1) subjects were evaluated according to the study treatment they have been assigned to; and 2) all available data were included. | |

### Primary: Change from baseline to Week 16 in pulmonary vascular resistance (PVR) at rest.

| | |
|---|---|
| End point title | Change from baseline to Week 16 in pulmonary vascular resistance (PVR) at rest. |
| End point description: | |
| The primary efficacy endpoint is defined as the PVR at rest at Week 16 expressed as percent of baseline PVR at rest. Full analysis set included all subjects assigned to a study treatment. | |
| End point type | Primary |
| End point timeframe: | |
| From baseline to Week 16 | |

| End point values | Macitentan | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 40 | 40 | | |
| Units: % of PVR at baseline (=100%) | | | | |
| geometric mean (confidence interval 95%) | 73.0 (63.6 to 83.8) | 87.2 (78.5 to 96.7) | | |

### Statistical analyses

| Statistical analysis title | Analysis of change in PVR |
|---|---|
| Statistical analysis description: | |
| The null hypothesis (change of PVR at rest in Week 16 in percent of baseline PVR in subjects treated with placebo or macitentan is the same) is tested on the primary endpoint by means of an analysis of covariance (ANCOVA) model on the log(e) transformed % of baseline PVR at rest at Week 16. | |
| Comparison groups | Macitentan v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[1] |
| P-value | = 0.041 |
| Method | ANCOVA |
| Parameter estimate | ratio of geometric means |
| Point estimate | 0.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 0.99 |

Notes:

[1] - ANCOVA model on log-transformed % of baseline PVR at Week 16 adjusted by treatment as a factor and log transformed PVR at baseline as a covariate.

## Secondary: Change from baseline to Week 24 in exercise capacity, as measured by the 6-minute walk distance (6MWD).

| | |
|---|---|
| End point title | Change from baseline to Week 24 in exercise capacity, as measured by the 6-minute walk distance (6MWD). |

End point description:

The purpose of the six minute walk is to test exercise tolerance and capacity. The test measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface. The goal is for the individual to walk as far as possible in six minutes. Full analysis set included all subjects assigned to a study treatment.

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

End point timeframe:

From baseline to Week 24

| **End point values** | Macitentan | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 40 | 40 | | |
| Units: meter | | | | |
| arithmetic mean (standard deviation) | | | | |
| 6MWD (m) at baseline | 353.0 (± 87.90) | 351.2 (± 73.79) | | |
| 6MWD (m) at Week 24 | 388.0 (± 83.31) | 352.2 (± 121.29) | | |
| Change from baseline to Week 24 | 35.0 (± 52.52) | 1.0 (± 83.24) | | |

## Statistical analyses

| **Statistical analysis title** | Analysis of change in 6MWD |
|---|---|

Statistical analysis description:

Statistical model is ANCOVA including 6MWD at baseline as a covariate, with treatment as factor in the model. The least squares (LS) mean difference of change from baseline to Week 24 (treatment difference: macitentan vs placebo) was 34.04 m (95% confidence limit: 2.9, 65.2, p = 0.0326).

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

| | |
|---|---|
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[2] |
| P-value | = 0.0326 |
| Method | ANCOVA |
| Parameter estimate | Least square (LS) mean difference |
| Point estimate | 34.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.9 |
| upper limit | 65.2 |

Notes:

[2] - To control for multiplicity across primary and secondary endpoints, all secondary endpoints were analyzed in sequence using hierarchical approach based on order and significance as pre-specified in protocol eliminating further adjustment for multiple comparisons.

## Secondary: Change from baseline to Week 24 in Borg dyspnea index collected at the end of the 6-minute walk test (6MWT).

| | |
|---|---|
| End point title | Change from baseline to Week 24 in Borg dyspnea index collected at the end of the 6-minute walk test (6MWT). |

End point description:

This outcome measures the difference in the Borg dyspnea index at Week 24 compared to baseline. The index rates the severity of dyspnea (difficult or labored breathing) on a scale from 0 ('Nothing at all') to 10 ('Very, very severe – maximal'). Full analysis set included all subjects assigned to a study treatment.

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

End point timeframe:

From baseline to Week 24

| **End point values** | Macitentan | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 40 | 40 | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Borg dyspnea index score at baseline | 4.2 (± 2.52) | 4.2 (± 2.14) | | |
| Borg dyspnea index score at Week 24 | 4.1 (± 2.52) | 4.4 (± 2.45) | | |
| Change from baseline to Week 24 | -0.1 (± 1.86) | 0.3 (± 2.04) | | |

## Statistical analyses

| **Statistical analysis title** | Analysis of change in Borg dyspnea index |
|---|---|

Statistical analysis description:

Statistical model is Analysis of Covariance including Borg dyspnea index at baseline as a covariate, with Treatment as factor in the model. The least squares (LS) mean difference of change from baseline to Week 24 (macitentan vs placebo) was -0.39 (95% confidence limit: –1.21, 0.43; p=0.3492).

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

| | |
|---|---|
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[3] |
| P-value | = 0.3492 |
| Method | ANCOVA |
| Parameter estimate | Least square (LS) mean difference |
| Point estimate | -0.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.21 |
| upper limit | 0.43 |

Notes:

[3] - To control for multiplicity across primary and secondary endpoints, all secondary endpoints were analyzed in sequence using hierarchical approach based on order and significance as pre-specified in protocol eliminating further adjustment for multiple comparisons.

## Secondary: Proportion of subjects with worsening in WHO functional class from baseline to Week 24.

| | |
|---|---|
| End point title | Proportion of subjects with worsening in WHO functional class from baseline to Week 24. |

End point description:

WHO functional classes are defined as follows: 1) class I: no symptoms with exercise or at rest. No limitation of activity. 2) class II: No symptoms at rest but slight limitation with ordinary activities causing symptoms (e.g. short of breath with climbing a flight of stairs, grocery shopping, or making the bed). 3) class III: may not have symptoms at rest but activities greatly limited by shortness of breath, fatigue, or near fainting. 4) class IV: symptoms at rest (such as dyspnea and/or fatigue) and inability to carry out any physical activity without symptoms (e.g. may faint especially while bending over with their heads lowered). Patients in class IV manifest signs of right heart failure. Shifting to a higher class (e.g. from class III to class IV) represents a 'worsening' while shifting to a lower class (e.g. from class III to class II) means an 'improvement'. Full analysis set included all subjects assigned to a study treatment.

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

End point timeframe:

From baseline to Week 24

| **End point values** | Macitentan | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 40 | 40 | | |
| Units: Subjects | | | | |
| WHO functional class I at baseline | 0 | 0 | | |
| WHO functional class II at baseline | 12 | 6 | | |
| WHO functional class III at baseline | 28 | 33 | | |
| WHO functional class IV at baseline | 0 | 1 | | |
| WHO functional class I at Week 24 | 3 | 1 | | |
| WHO functional class II at Week 24 | 15 | 10 | | |
| WHO functional class III at Week 24 | 22 | 26 | | |
| WHO functional class IV at Week 24 | 0 | 3 | | |
| Worsened | 0 | 3 | | |
| Not worsened (total) | 40 | 37 | | |
| Not worsened (unchanged) | 31 | 29 | | |
| Not worsened (improved) | 9 | 8 | | |

## Statistical analyses

| **Statistical analysis title** | Analysis of worsening in WHO functional class |
|---|---|

Statistical analysis description:

The null hypothesis is odds of worsening are the same in placebo and macitentan group. Logistic regression is used for macitentan vs placebo comparison with treatment and WHO functional class at baseline as factors in the model. The odds ratio for worsening WHO functional class at Week 24 (macitentan vs placebo) was 0.212 (95% confidence limit: < 0.001, 1.464, p = 0.0962).

| | |
|---|---|
| Comparison groups | Macitentan v Placebo |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[4] |
| P-value | = 0.0962 |
| Method | ANCOVA |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.212 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.001 |
| upper limit | 1.464 |

Notes:

[4] - To control for multiplicity across primary and secondary endpoints, all secondary endpoints were analyzed in sequence using hierarchical approach based on order and significance as pre-specified in protocol eliminating further adjustment for multiple comparisons.

## Post-hoc: Post-hoc analysis of change from baseline to Week 16 in Pulmonary Vascular Resistance (PVR) at rest including subjects with corrected hemodynamic values

| End point title | Post-hoc analysis of change from baseline to Week 16 in Pulmonary Vascular Resistance (PVR) at rest including subjects with corrected hemodynamic values |
|---|---|

End point description:

The main analysis of the primary efficacy endpoint of PVR was repeated after the voluntary right heart catheterization source data verification (SDV) and independent medical review of hemodynamic data corrected for 13 subjects reported after the clinical database closure. Full analysis set for this post-hoc analysis included all subjects assigned to a study treatment with SDV values.

| End point type | Post-hoc |
|---|---|

End point timeframe:

From baseline to Week 16

| End point values | Macitentan | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 40 | 40 | | |
| Units: Percent of baseline PVR | | | | |
| geometric mean (confidence interval 95%) | 71.5 (63.5 to 80.4) | 87.6 (79.0 to 97.2) | | |

### Statistical analyses

| Statistical analysis title | Analysis of PVR change with corrected PVR values |
|---|---|

Statistical analysis description:

The same statistical model as for the predefined analysis (ANCOVA) was applied, including 13 subjects with corrected hemodynamic values.

| | |
|---|---|
| Comparison groups | Macitentan v Placebo |
| Number of subjects included in analysis | 80 |
| Analysis specification | Post-hoc |
| Analysis type | superiority[5] |
| P-value | = 0.0098 [6] |
| Method | ANCOVA |
| Parameter estimate | Model-adjusted geometric mean ratio |
| Point estimate | 0.81 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 0.95 |

Notes:

[5] - ANCOVA model on log-transformed % of baseline PVR at Week 16 adjusted by treatment as a factor and log transformed PVR at baseline as a covariate.

[6] - This is the post-hoc analysis and p-value is an exploratory p-value.

### Post-hoc: Post-hoc Analysis of change from baseline to Week 16 in Pulmonary Vascular Resistance (PVR) at rest Excluding Subjects with Corrected Hemodynamic Values

| End point title | Post-hoc Analysis of change from baseline to Week 16 in Pulmonary Vascular Resistance (PVR) at rest Excluding Subjects with Corrected Hemodynamic Values |
|---|---|

End point description:

The main analysis of the primary efficacy endpoint of PVR was repeated which excluded data for 13 subjects with corrected hemodynamic values. The hemodynamic values were reported after the SDV assessment clinical database closure. Full analysis set excluding subjects with corrected hemodynamic values.

| End point type | Post-hoc |
|---|---|

End point timeframe:

From baseline to Week 16

| End point values | Macitentan | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 34 | | |
| Units: Percent of baseline PVR | | | | |
| geometric mean (confidence interval 95%) | 68.4 (60.3 to 77.5) | 86.1 (77.3 to 95.7) | | |

**Statistical analyses**

| Statistical analysis title | Post-hoc statistical analysis 1 |
|---|---|
| Comparison groups | Macitentan v Placebo |
| Number of subjects included in analysis | 67 |
| Analysis specification | Post-hoc |
| Analysis type | superiority[7] |
| P-value | = 0.0061 [8] |
| Method | ANCOVA |
| Parameter estimate | Model-adjusted geometric mean ratio |
| Point estimate | 0.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.68 |
| upper limit | 0.93 |

Notes:

[7] - ANCOVA model on log-transformed % of baseline PVR at Week 16 adjusted by treatment as a factor and log transformed PVR at baseline as a covariate.
[8] - This is the post-hoc analysis and p-value is an exploratory p-value.

**Post-hoc: Post-hoc Analysis of change from baseline to Week 16 in Pulmonary Vascular Resistance (PVR) at rest Excluding Subjects with Implausible Hemodynamic Findings**

| End point title | Post-hoc Analysis of change from baseline to Week 16 in Pulmonary Vascular Resistance (PVR) at rest Excluding Subjects with Implausible Hemodynamic Findings |
|---|---|

End point description:

The main analysis of the primary efficacy endpoint of PVR was repeated which excluded 14 subjects with implausible hemodynamic findings. Full analysis set excluding subjects with implausible hemodynamic findings.

| End point type | Post-hoc |
|---|---|

End point timeframe:

From baseline to Week 16

| End point values | Macitentan | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 34 | | |
| Units: Percent of baseline PVR | | | | |
| geometric mean (confidence interval 95%) | 73.9 (66.2 to 82.4) | 86.6 (77.9 to 96.4) | | |

### Statistical analyses

| **Statistical analysis title** | Post-hoc statistical analysis 1 |
|---|---|
| Comparison groups | Macitentan v Placebo |
| Number of subjects included in analysis | 66 |
| Analysis specification | Post-hoc |
| Analysis type | superiority[9] |
| P-value | = 0.0414 [10] |
| Method | ANCOVA |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 0.99 |

Notes:

[9] - ANCOVA model on log-transformed % of baseline PVR at Week 16 adjusted by treatment as a factor and log transformed PVR at baseline as a covariate.
[10] - This is the post-hoc analysis and p-value is an exploratory p-value.

### Post-hoc: Post-hoc Analysis of Change from baseline to Week 24 in exercise capacity, as measured by the 6-minute walk distance (6MWD) Excluding subjects with Implausible Hemodynamic Findings

| End point title | Post-hoc Analysis of Change from baseline to Week 24 in exercise capacity, as measured by the 6-minute walk distance (6MWD) Excluding subjects with Implausible Hemodynamic Findings |
|---|---|

End point description:

The same analysis for the secondary endpoint, 6MWD, is repeated on the full analysis set excluding 14 subject with implausible hemodynamic findings. Full analysis set excluding subjects with implausible hemodynamic findings.

| End point type | Post-hoc |
|---|---|

End point timeframe:

From baseline to Week 24

| **End point values** | Macitentan | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 34 | | |
| Units: meter | | | | |
| least squares mean (confidence interval 95%) | 37.41 (11.12 to 63.71) | 0.23 (-25.28 to 25.74) | | |

## Statistical analyses

| **Statistical analysis title** | Post-hoc statistical analysis 1 |
|---|---|

Statistical analysis description:

Statistical model is ANCOVA including 6MWD at baseline as a covariate, with treatment as factor in the model.

| | |
|---|---|
| Comparison groups | Macitentan v Placebo |
| Number of subjects included in analysis | 66 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | = 0.0468 [11] |
| Method | ANCOVA |
| Parameter estimate | least squares (LS) mean difference |
| Point estimate | 37.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 73.83 |

Notes:

[11] - This is the post-hoc analysis and p-value is an exploratory p-value.

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| From double-blind 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 | Macitentan |
| Reporting group description: | |
| Macitentan 10 mg, oral tablet, to be taken once daily. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Matching placebo oral tablet, to be taken once daily. | |

| Serious adverse events | Macitentan | Placebo | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 40 (7.50%) | 7 / 40 (17.50%) | |
| number of deaths (all causes) | 0 | 2 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| Weight increased | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Embolism | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac disorders | | | |
| Acute right ventricular failure | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | 0 / 40 (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 / 40 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Right ventricular failure | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 2 / 40 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| General disorders and administration site conditions | | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | 0 / 40 (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 | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 2 / 40 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 40 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 1 / 40 (2.50%) | |
| 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** | Macitentan | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 22 / 40 (55.00%) | 19 / 40 (47.50%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 3 / 40 (7.50%) | |
| occurrences (all) | 0 | 4 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 3 / 40 (7.50%) | |
| occurrences (all) | 0 | 4 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 6 / 40 (15.00%) | 0 / 40 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 2 / 40 (5.00%) | |
| occurrences (all) | 0 | 2 | |
| Cardiac disorders | | | |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 2 / 40 (5.00%) | |
| occurrences (all) | 0 | 2 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 2 | 1 | |

| | | | |
|---|---|---|---|
| Syncope | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 3 / 40 (7.50%) | |
| occurrences (all) | 0 | 3 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | 0 / 40 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 8 / 40 (20.00%) | 4 / 40 (10.00%) | |
| occurrences (all) | 10 | 4 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | 3 / 40 (7.50%) | |
| occurrences (all) | 2 | 3 | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 2 | 1 | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | 2 / 40 (5.00%) | |
| occurrences (all) | 1 | 2 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 2 / 40 (5.00%) | |
| occurrences (all) | 0 | 2 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | 3 / 40 (7.50%) | |
| occurrences (all) | 1 | 3 | |
| Back pain | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 2 / 40 (5.00%) | |
| occurrences (all) | 0 | 2 | |
| Bone pain | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | 0 / 40 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Pain in extremity | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 40 (7.50%) | 0 / 40 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | 4 / 40 (10.00%) | |
| occurrences (all) | 1 | 4 | |
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | 0 / 40 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 2 / 40 (5.00%) | |
| occurrences (all) | 0 | 2 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 40 (7.50%) | 0 / 40 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 2 | 1 | |
| Metabolism and nutrition disorders | | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 2 / 40 (5.00%) | |
| occurrences (all) | 0 | 2 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 25 March 2015 | Global amendment 1 resulting in Protocol version 2. Changes included: - Number of study countries screening period was prolonged to improve the rate of recruitment. - Modification of the required qualifications for country-specific adjudication committees (CSAC). - Further clarification of guidelines on oxygen use during the 6MWT. - Clarification of use of the PAH-SYMPACT questionnaire. - Update of ICF to reflect changes in country numbers and of clarifications of study procedures in clinical protocol. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

### Online references

http://www.ncbi.nlm.nih.gov/pubmed/28919201