# Clinical trial results:
# A randomized, double-blind, placebo-controlled, prospective, multicenter, parallel group study to assess the safety and efficacy of macitentan in patients with portopulmonary hypertension

## Summary

| | |
|---|---|
| EudraCT number | 2014-004624-21 |
| Trial protocol | GB DE CZ ES FR |
| Global end of trial date | |

### Results information

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 09 November 2018 |
| First version publication date | 09 November 2018 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | AC-055-404 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02382016 |
| 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@its.jnj.com |
| Scientific contact | Clinical Trial Disclosure Desk, ACTELION Pharmaceuticals Ltd., clinical-trials-disclosure@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 | Interim |
| Date of interim/final analysis | 06 April 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 25 October 2017 |
| Global end of trial reached? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the effect of macitentan on pulmonary vascular resistance (PVR) as compared to placebo in patients with portopulmonary hypertension (PoPH).

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. 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:

As per randomization stratification, 63.5% of patients (54 out of 85 patients) were receiving a pulmonary arterial hypertension (PAH)-specific therapy at baseline.

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 23 June 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Brazil: 5 |
| Country: Number of subjects enrolled | Czech Republic: 4 |
| Country: Number of subjects enrolled | France: 39 |
| Country: Number of subjects enrolled | Germany: 8 |
| Country: Number of subjects enrolled | Spain: 4 |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Country: Number of subjects enrolled | United States: 23 |
| Worldwide total number of subjects | 85 |
| EEA total number of subjects | 57 |

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) | 64 |
| From 65 to 84 years | 21 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Patients  at 39 sites in 7 countries were screened and were randomized at 36 sites in these 7 countries (Brazil, Czech Republic, France, Germany, Spain, UK and US).

### Pre-assignment

Screening details:

A total of 119 patients were screened and off these, 85 patients at were randomized (43 to macitentan 10 mg once daily and 42 to matching placebo) and received double-blind (DB) study treatment. Overall, 80 patients who completed the DB treatment period entered the open-label treatment period.

### Period 1

| | |
|---|---|
| Period 1 title | DB treatment period (overall 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 10 mg |

Arm description:

Macitentan 10 mg to be taken once daily, oral use, film-coated tablet

| | |
|---|---|
| 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:

Macitentan 10 mg to be taken once daily

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

Arm description:

Macitentan-matching placebo to be taken once daily, oral use, film-coated tablet

| | |
|---|---|
| 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:

Macitentan-matching placebo to be taken once daily

| **Number of subjects in period 1** | Macitentan 10 mg | Placebo |
|---|---|---|
| Started | 43 | 42 |
| Completed | 39 | 41 |
| Not completed | 4 | 1 |
| Physician decision | 3 | - |
| Consent withdrawn by subject | - | 1 |
| Lack of efficacy | 1 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Macitentan 10 mg |
| Reporting group description: | |
| Macitentan 10 mg to be taken once daily, oral use, film-coated tablet | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Macitentan-matching placebo to be taken once daily, oral use, film-coated tablet | |

| Reporting group values | Macitentan 10 mg | Placebo | Total |
|---|---|---|---|
| Number of subjects | 43 | 42 | 85 |
| Age categorical<br>Units: Subjects | | | |
| < 65 years | 35 | 29 | 64 |
| ≥ 65 years | 8 | 13 | 21 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 58.0 | 59.0 | |
| standard deviation | ± 8.7 | ± 9.5 | - |
| Gender categorical<br>Units: | | | |
| Female | 21 | 20 | 41 |
| Male | 22 | 22 | 44 |
| Enrollment by geographical region<br>Units: Subjects | | | |
| Europe | 29 | 28 | 57 |
| North America | 12 | 11 | 23 |
| Latin America | 2 | 3 | 5 |
| Race<br>Units: Subjects | | | |
| Asian | 1 | 0 | 1 |
| White | 23 | 21 | 44 |
| Other | 1 | 0 | 1 |
| Not Applicable | 18 | 21 | 39 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 6 | 6 | 12 |
| Not Hispanic or Latino | 19 | 15 | 34 |
| Missing | 18 | 21 | 39 |
| PAH-specific therapy<br>Units: Subjects | | | |
| Yes | 27 | 27 | 54 |
| No | 16 | 15 | 31 |
| Body Mass Index (BMI)<br>Units: kg/m2 | | | |
| arithmetic mean | 29.01 | 29.33 | |
| standard deviation | ± 4.79 | ± 4.04 | - |
| Time since portal hypertension diagnosis | | | |

| | | | |
|---|---|---|---|
| Units: months | | | |
| median | 23 | 31 | |
| inter-quartile range (Q1-Q3) | 5 to 80 | 4 to 69 | - |
| Time since PAH diagnosis | | | |
| Units: months | | | |
| median | 7 | 12 | |
| inter-quartile range (Q1-Q3) | 2 to 33 | 1 to 37 | - |
| Pulmonary vascular resistance (PVR) at baseline (calculated) | | | |
| Units: dyn*sec/cm5 | | | |
| arithmetic mean | 552.4 | 521.7 | |
| standard deviation | ± 192.8 | ± 163.3 | - |

## 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) includes all randomized patients who received at least one dose of study treatment in the DB treatment period and have a baseline value for the primary endpoint (pulmonary vascular resistance). Subjects are evaluated according to the treatment to which they were assigned (which may be different from the treatment they have received).

| **Reporting group values** | Full analysis set (FAS) | | |
|---|---|---|---|
| Number of subjects | 85 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| < 65 years | 64 | | |
| ≥ 65 years | 21 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 58.5 | | |
| standard deviation | ± 9.1 | | |
| Gender categorical | | | |
| Units: | | | |
| Female | 41 | | |
| Male | 44 | | |
| Enrollment by geographical region | | | |
| Units: Subjects | | | |
| Europe | 57 | | |
| North America | 23 | | |
| Latin America | 5 | | |
| Race | | | |
| Units: Subjects | | | |
| Asian | 1 | | |
| White | 44 | | |
| Other | 1 | | |
| Not Applicable | 29 | | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 12 | | |
| Not Hispanic or Latino | 34 | | |

| | | | |
|---|---|---|---|
| Missing | 39 | | |
| PAH-specific therapy<br>Units: Subjects | | | |
| Yes | 54 | | |
| No | 31 | | |
| Body Mass Index (BMI)<br>Units: kg/m2 | | | |
| arithmetic mean | 29.17 | | |
| standard deviation | ± 4.41 | | |
| Time since portal hypertension diagnosis<br>Units: months | | | |
| median | 25 | | |
| inter-quartile range (Q1-Q3) | 5 to 76 | | |
| Time since PAH diagnosis<br>Units: months | | | |
| median | 10 | | |
| inter-quartile range (Q1-Q3) | 2 to 36 | | |
| Pulmonary vascular resistance (PVR) at baseline (calculated)<br>Units: dyn*sec/cm5 | | | |
| arithmetic mean | 537.2 | | |
| standard deviation | ± 178.4 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Macitentan 10 mg |
| Reporting group description: | |
| Macitentan 10 mg to be taken once daily, oral use, film-coated tablet | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Macitentan-matching placebo to be taken once daily, oral use, film-coated tablet | |
| Subject analysis set title | Full analysis set (FAS) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| The Full Analysis Set (FAS) includes all randomized patients who received at least one dose of study treatment in the DB treatment period and have a baseline value for the primary endpoint (pulmonary vascular resistance). Subjects are evaluated according to the treatment to which they were assigned (which may be different from the treatment they have received). | |

### Primary: Change from baseline to Week 12 in pulmonary vascular resistance (PVR)

| | |
|---|---|
| End point title | Change from baseline to Week 12 in pulmonary vascular resistance (PVR) |
| End point description: | |
| The relative change from baseline to Week 12 in PVR is expressed as a ratio of Week 12 to baseline PVR. | |
| End point type | Primary |
| End point timeframe: | |
| From enrollment/baseline to Week 12 in the DB treatment period | |

| End point values | Macitentan 10 mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 | 42 | | |
| Units: ratio of baseline PVR | | | | |
| geometric mean (confidence interval 95%) | 0.63 (0.58 to 0.67) | 0.98 (0.91 to 1.05) | | |

### Statistical analyses

| Statistical analysis title | Analysis of change in PVR |
|---|---|
| Statistical analysis description: | |
| The null hypothesis (change of PVR at Week 12 as a ratio 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 ratios of PVR at Week 12 to baseline PVR. | |
| Comparison groups | Macitentan 10 mg v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[1] |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | ratio of geometric means |
| Point estimate | 0.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.59 |
| upper limit | 0.72 |

Notes:

[1] - ANCOVA model adjusted by treatment, background PAH-specific therapy at baseline and region as factors, and log-transformed PVR at baseline as a covariate.

## Secondary: Change from baseline to Week 12 in 6-minute walk distance (6MWD)

| | |
|---|---|
| End point title | Change from baseline to Week 12 in 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.

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

End point timeframe:

From enrollment/baseline to Week 12 in the DB treatment period

| End point values | Macitentan 10 mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 | 42 | | |
| Units: meter | | | | |
| arithmetic mean (standard deviation) | | | | |
| 6MWD at baseline | 385.8 (± 99.97) | 383.2 (± 108.90) | | |
| 6MWD at Week 12 | 392.2 (± 98.46) | 380.8 (± 114.98) | | |
| Change of 6MWD from baseline to Week 12 | 6.4 (± 65.74) | -2.4 (± 43.65) | | |

### Statistical analyses

| Statistical analysis title | Analysis of change in 6MWD at Week 12 |
|---|---|
| Comparison groups | Macitentan 10 mg v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[2] |
| P-value | = 0.4264 [3] |
| Method | mixed-effect model repeated measure |
| Parameter estimate | Least squares (LS) mean difference |
| Point estimate | 9.73 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.5 |
| upper limit | 33.95 |

Notes:

[2] - The main analysis on 6MWD was performed using a mixed-effect model repeated measure (MMRM) adjusted for treatment, visit, region, PAH-specific therapy at baseline, and treatment-by-visit interaction as factors, and baseline 6MWD and WHO functional class (FC) as covariates.

[3] - No adjustment was made for multiplicity for secondary endpoints, therefore all corresponding p-values provided are of an exploratory nature.

## Secondary: Change from baseline to Week 12 in WHO functional class (FC)

| | |
|---|---|
| End point title | Change from baseline to Week 12 in WHO functional class (FC) |

End point description:

Changes from baseline to Week 12 in WHO FC were dichotomized as worsening (i.e., change > 0) versus no change or improvement (i.e., change ≤ 0). Class I: no symptoms with exercise or at rest. No limitation of activity. 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). Class III: may not have symptoms at rest but activities greatly limited by shortness of breath, fatigue, or near fainting. Class IV: symptoms at rest (e.g. dyspnea and/or fatigue) and inability to carry out any physical activity without symptoms. Patients in class IV manifest signs of right heart failure.

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

End point timeframe:

From enrollment/baseline to Week 12 in the DB treatment period

| End point values | Macitentan 10 mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 | 42 | | |
| Units: subjects | | | | |
| WHO FC I at baseline | 1 | 1 | | |
| WHO FC II at baseline | 27 | 23 | | |
| WHO FC III at baseline | 15 | 18 | | |
| WHO FC IV at baseline | 0 | 0 | | |
| WHO FC I at Week 12 | 3 | 4 | | |
| WHO FC II at Week 12 | 27 | 23 | | |
| WHO FC III at Week 12 | 13 | 15 | | |
| WHO FC IV at Week 12 | 0 | 0 | | |
| Improved from baseline to Week 12 | 9 | 7 | | |
| Worsened from baseline to Week 12 | 6 | 1 | | |
| Unchanged from baseline to Week 12 | 28 | 34 | | |

### Statistical analyses

| Statistical analysis title | Analysis of worsening in WHO FC at Week 12 |
|---|---|

Statistical analysis description:

A logistic regression model (exact) adjusted for treatment, PAH-specific therapy at baseline, and region as covariates was used to analyze worsening in WHO FC.

| | |
|---|---|
| Comparison groups | Macitentan 10 mg v Placebo |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1278 [4] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 6.253 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.714 |
| upper limit | 298.376 |

Notes:

[4] - No adjustment was made for multiplicity for secondary endpoints, therefore all corresponding p-values provided are of an exploratory nature.

### Secondary: Change from baseline to Week 12 in the biomarker N-terminal pro b-type natriuretic peptide (NT-proBNP)

| End point title | Change from baseline to Week 12 in the biomarker N-terminal pro b-type natriuretic peptide (NT-proBNP) |
|---|---|

End point description:

NT-proBNP functions as a strong indicator of prognosis in patients with pulmonary hypertension (PH). The relative change from baseline to Week 12 in NT-proBNP is expressed as a ratio of Week 12 to baseline NT-proBNP.

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

End point timeframe:

From enrollment/baseline to Week 12 in the DB treatment period

| End point values | Macitentan 10 mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 41 | 40 | | |
| Units: ratio of baseline NT-proBNP | | | | |
| geometric mean (confidence interval 95%) | 0.86 (0.67 to 1.11) | 1.04 (0.81 to 1.34) | | |

## Statistical analyses

| Statistical analysis title | Analysis of change in NT-proBNP |
|---|---|
| Comparison groups | Macitentan 10 mg v Placebo |
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3951 [5] |
| Method | ANCOVA |
| Parameter estimate | ratio of geometric means |
| Point estimate | 0.874 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.639 |
| upper limit | 1.196 |

Notes:

[5] - No adjustment was made for multiplicity for secondary endpoints, therefore all corresponding p-values provided are of an exploratory nature.

## Secondary: Change from baseline to Week 12 in mean right atrial pressure (mRAP)

| End point title | Change from baseline to Week 12 in mean right atrial pressure (mRAP) |
|---|---|

End point description:

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

End point timeframe:

From enrollment/baseline to Week 12 in the DB treatment period

| End point values | Macitentan 10 mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 42 | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| mRAP at baseline | 7.3 (± 3.74) | 6.7 (± 3.60) | | |
| mRAP at Week 12 | 9.0 (± 5.32) | 7.0 (± 2.93) | | |
| Change in mRAP from baseline to Week 12 | 1.6 (± 5.55) | 0.3 (± 3.29) | | |

## Statistical analyses

| Statistical analysis title | Analysis of change in mRAP |
|---|---|
| Comparison groups | Macitentan 10 mg v Placebo |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0637 [6] |
| Method | ANCOVA |
| Parameter estimate | Least squares (LS) mean difference |
| Point estimate | 1.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.1 |
| upper limit | 3.44 |

Notes:

[6] - No adjustment was made for multiplicity for secondary endpoints, therefore all corresponding p-values provided are of an exploratory nature.

## Secondary: Change from baseline to Week 12 in mean pulmonary artery pressure (mPAP)

| End point title | Change from baseline to Week 12 in mean pulmonary artery pressure (mPAP) |
|---|---|

End point description:

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

End point timeframe:

From enrollment/baseline to Week 12 in the DB treatment period

| End point values | Macitentan 10 mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 | 42 | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| mPAP at baseline | 46.4 (± 7.89) | 43.8 (± 8.52) | | |
| mPAP at Week 12 | 40.0 (± 7.61) | 44.2 (± 8.26) | | |
| Change in mPAP at Week 12 | -6.4 (± 4.94) | 0.4 (± 7.04) | | |

## Statistical analyses

| Statistical analysis title | Analysis of change in mPAP |
|---|---|
| Comparison groups | Macitentan 10 mg v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [7] |
| Method | ANCOVA |
| Parameter estimate | Least squares (LS) mean difference |
| Point estimate | -5.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.4 |
| upper limit | -3.57 |

Notes:

[7] - No adjustment was made for multiplicity for secondary endpoints, therefore all corresponding p-values provided are of an exploratory nature.

## Secondary: Change from baseline to Week 12 in cardiac index

| | |
|---|---|
| End point title | Change from baseline to Week 12 in cardiac index |

End point description:

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

End point timeframe:

From enrollment/baseline to Week 12 in the DB treatment period

| End point values | Macitentan 10 mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 | 42 | | |
| Units: L/min/m2 | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cardiac index at baseline | 3.1 (± 0.83) | 2.9 (± 0.76) | | |
| Cardiac index at Week 12 | 3.7 (± 1.04) | 3.0 (± 0.82) | | |
| Change in Cardiac index at Week 12 | 0.6 (± 0.8) | 0.1 (± 0.6) | | |

### Statistical analyses

| Statistical analysis title | Analysis of change in cardiac index |
|---|---|
| Comparison groups | Macitentan 10 mg v Placebo |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0009 [8] |
| Method | ANCOVA |
| Parameter estimate | Least squares (LS) mean difference |
| Point estimate | 0.52 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.22 |
| upper limit | 0.81 |

Notes:

[8] - No adjustment was made for multiplicity for secondary endpoints, therefore all corresponding p-values provided are of an exploratory nature.

## Secondary: Change from baseline to Week 12 in total pulmonary resistance (TPR)

| | |
|---|---|
| End point title | Change from baseline to Week 12 in total pulmonary resistance (TPR) |

End point description:

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

End point timeframe:

From enrollment/baseline to Week 12 in the DB treatment period

| **End point values** | Macitentan 10 mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 | 42 | | |
| Units: dyn*sec/cm5 | | | | |
| arithmetic mean (standard deviation) | | | | |
| TPR at baseline | 689.3 (± 228.59) | 671.5 (± 199.73) | | |
| TRP at Week 12 | 489.4 (± 157.13) | 653.1 (± 197.88) | | |
| Change in TPR from baseline to Week 12 | -199.8 (± 163.06) | -18.3 (± 135.28) | | |

### Statistical analyses

| **Statistical analysis title** | Analysis of change in TPR |
|---|---|
| Comparison groups | Macitentan 10 mg v Placebo |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [9] |
| Method | ANCOVA |
| Parameter estimate | Least squares (LS) mean difference |
| Point estimate | -171.48 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -223.67 |
| upper limit | -119.3 |

Notes:

[9] - No adjustment was made for multiplicity for secondary endpoints, therefore all corresponding p-values provided are of an exploratory nature.

## Secondary: Change from baseline to Week 12 in mixed venous oxygen saturation (SVO2)

| End point title | Change from baseline to Week 12 in mixed venous oxygen saturation (SVO2) |
|---|---|

End point description:

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

End point timeframe:

From enrollment/baseline to Week 12 in the DB treatment period

| **End point values** | Macitentan 10 mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 41 | 41 | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | | | | |
| SVO2 at baseline | 69.2 (± 9.87) | 69.9 (± 5.34) | | |
| SVO2 at Week 12 | 70.3 (± 7.07) | 70.7 (± 8.58) | | |
| Change in SVO2 from baseline to Week 12 | 1.1 (± 6.70) | 0.8 (± 7.81) | | |

### Statistical analyses

| **Statistical analysis title** | Analysis of change in SVO2 |
|---|---|
| Comparison groups | Macitentan 10 mg v Placebo |
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9844 [10] |
| Method | ANCOVA |
| Parameter estimate | Least squares (LS) mean difference |
| Point estimate | 0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.85 |
| upper limit | 2.91 |

Notes:

[10] - No adjustment was made for multiplicity for secondary endpoints, therefore all corresponding p-values provided are of an exploratory nature.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From double-blind study treatment initiation up to 30 days after study treatment discontinuation or start of open label period

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Macitentan 10 mg |

Reporting group description:

Macitentan 10 mg to be taken once daily, film-coated tablet, oral use

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

Reporting group description:

Macitentan-matching placebo to be taken once daily, film-coated tablet, oral use

| Serious adverse events | Macitentan 10 mg | Placebo | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 43 (20.93%) | 6 / 42 (14.29%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Hepatocellular carcinoma | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 2 / 42 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Aneurysm repair | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | 1 / 42 (2.38%) | |
| 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 | | | |
| Localised oedema | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 42 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 42 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 42 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Alveolitis | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 42 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthma | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 42 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 42 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary arterial hypertension | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 42 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary toxicity | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 42 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Troponin I increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 42 (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 | | | |
| Vascular procedure complication | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | 1 / 42 (2.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 42 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular failure | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 42 (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 | 2 / 43 (4.65%) | 1 / 42 (2.38%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 42 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 42 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 42 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 42 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 42 (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 | 1 / 43 (2.33%) | 1 / 42 (2.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Localised infection | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | 1 / 42 (2.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 42 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 42 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Fluid overload | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 0 / 42 (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: 5 %

| **Non-serious adverse events** | Macitentan 10 mg | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 22 / 43 (51.16%) | 22 / 42 (52.38%) | |
| Investigations | | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | 0 / 42 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 7 / 43 (16.28%) | 7 / 42 (16.67%) | |
| occurrences (all) | 10 | 8 | |
| General disorders and administration site conditions | | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 10 / 43 (23.26%) | 5 / 42 (11.90%) | |
| occurrences (all) | 13 | 6 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | 4 / 42 (9.52%) | |
| occurrences (all) | 1 | 6 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | 3 / 42 (7.14%) | |
| occurrences (all) | 0 | 3 | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | 5 / 42 (11.90%) | |
| occurrences (all) | 0 | 6 | |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | 3 / 42 (7.14%) | |
| occurrences (all) | 2 | 3 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 4 / 43 (9.30%) | 0 / 42 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 2 / 43 (4.65%)<br>2 | 6 / 42 (14.29%)<br>6 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 15 January 2015 | Amendment 1, resulting in Global Protocol Version 2:<br>• Visit window was changed to ± 4 days from ± 7 days to ensure patients had enough study treatment until the next visit.<br>• Reference to hepatic event questionnaire was removed as this form was removed from the electronic Case Report Form (eCRF)<br>• Daclatasvir was added as permitted Hepatitis C medication following its approval<br>• Analysis of urea was removed as it was not needed in addition to blood urea nitrogen.<br>• NT-proBNP storage/shipping text was further clarified<br>• It was clarified that laboratory assessments to be used for eligibility assessment were those performed at Visit 1 / Screening (not Visit 2 / Randomization).<br>• A urine dipstick pregnancy test was added to the assessments at Visit 2 / Randomization in order to have the result prior to treatment assignment.<br>• It was clarified that hepatic vein catheterization (HVC) was not mandatory<br>• It was clarified that PAH or PoPH medications stopped within 3 months prior to randomization were required to be documented in the eCRF. |
| 21 April 2016 | Amendment 2, resulting in Global Protocol Version 3:<br>• It was clarified that local laboratory assessments were allowed in order to simplify eligibility assessment and implementation of the stopping rule (i.e., for calculating Model for End-Stage Liver Disease (MELD) score and/or Child-Pugh classification) at Week 12. It was further clarified that the central laboratory kit was required to be used in parallel to the use of local laboratory assessments.<br>• It was clarified that study treatment was allowed to be continued in case of orthotopic liver transplantation (OLT) during the OL period of the study, based on medical consideration.<br>• It was allowed to perform the pharmacokinetic (PK) substudy closer to the patient's home to ease participation<br>• Certain eligibility criteria were modified based on medical considerations, e.g., exclusion criterion 15: transplant expected within 3 months removed; exclusion 21: calcium channel blockers (CCBs) moved to exclusion 20; beta blockers moved to exclusion 10)<br>• The list of allowed and forbidden medications was updated with newly approved antiviral medications<br>• It was clarified that screening started on the day of ICF signature<br>• The definition of the Full Analysis Set was modified to include patients for whom post-baseline PVR was imputed |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported