



## 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	<ul style="list-style-type: none"><li>New data added to full data set</li></ul> FDS updated per CSR Addendum-2.

### Trial information

#### Trial identification

Sponsor protocol code	AC-055E201
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#### 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:

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### 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
<b>Arm title</b>	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

<b>Arm title</b>	Placebo
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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

<b>Number of subjects in period 1</b>	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
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Reporting group description:

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

Reporting group title	Placebo
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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/m <sup>2</sup>			
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/cm <sup>5</sup>			
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 standard deviation	1.5 ± 2.16		
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## 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 <sup>[1]</sup>
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).
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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
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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
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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
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Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority <sup>[2]</sup>
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

<b>End point values</b>	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**

<b>Statistical analysis title</b>	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 <sup>[3]</sup>
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.
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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
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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

<b>Statistical analysis title</b>	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 <sup>[4]</sup>
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 <sup>[5]</sup>
P-value	= 0.0098 <sup>[6]</sup>
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 <sup>[7]</sup>
P-value	= 0.0061 <sup>[8]</sup>
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
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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
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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

<b>Statistical analysis title</b>	Post-hoc statistical analysis 1
Comparison groups	Macitentan v Placebo
Number of subjects included in analysis	66
Analysis specification	Post-hoc
Analysis type	superiority <sup>[9]</sup>
P-value	= 0.0414 <sup>[10]</sup>
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
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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
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End point timeframe:

From baseline to Week 24

<b>End point values</b>	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

<b>Statistical analysis title</b>	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 <sup>[11]</sup>
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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19
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### Reporting groups

Reporting group title	Macitentan
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Reporting group description:

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

Reporting group title	Placebo
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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 %

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

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

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

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