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	v1
This version publication date	01 June 2018
First version publication date	18 October 2017

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	Safety, Efficacy
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	Investigator, Carer, Assessor, Subject

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 (which may be different from the study treatment they have received) 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 (which may be different from the study treatment they have received) 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.	
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 main analysis for the primary endpoint was the ANCOVA model on log-transformed percent of baseline PVR at Week 16 adjusted by treatment as a factor and log transformed PVR at baseline as a covariate. From the adjusted model, the treatment effect at Week 16 (ratio of geometric means macitentan/placebo) was 0.84 (95% confidence limit: 0.70, 0.99; p = 0.041).	
Comparison groups	Macitentan v Placebo

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.041
Method	ANCOVA

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:

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
P-value	= 0.0326
Method	ANCOVA

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').

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
P-value	= 0.3492
Method	ANCOVA

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:

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				
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:

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
P-value	= 0.0962
Method	ANCOVA

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_10_mg
Reporting group description:	
Reporting group 1 description	
Reporting group title	Placebo
Reporting group description:	
Reporting group 2 description	

Serious adverse events	Macitentan_10_mg	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_10_mg	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? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported