Clinical trial results:
A Prospective, Multicenter, Single-arm, Open-label, Phase 4 Study to Evaluate the Effects of Macitentan on Right vEntricular Remodeling in Pulmonary Arterlal HypeRtension Assessed by Cardiac Magnetic Resonance Imaging

Summary

EudraCT number	2014-004066-20
Trial protocol	GB NL DE IT
Global end of trial date	08 August 2019

Results information

Result version number	v1 (current)
This version publication date	20 September 2020
First version publication date	20 September 2020

Trial information

Trial identification

Sponsor protocol code	AC-055-403

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02310672
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceutical Ltd.
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, 4123
Public contact	Global Medical Information, Actelion Pharmaceutical Ltd., medinfo@actelion.com
Scientific contact	Global Medical Information, Actelion Pharmaceutical Ltd., medinfo@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	08 August 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to evaluate the effect of macitentan on right ventricular and on hemodynamic properties in subjects with symptomatic pulmonary arterial hypertension (PAH).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Safety was evaluated based on adverse events (AEs), clinical laboratory tests (hematology, serum chemistry, coagulation tests, and pregnancy test), vital sign measurements, and physical examinations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 June 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Ethical reason
Long term follow-up duration	13 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Hong Kong: 7
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Malaysia: 8
Country: Number of subjects enrolled	Netherlands: 12
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	Singapore: 9
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	87
EEA total number of subjects	44

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)	75
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total of 112 subjects was screened out of them 89 subjects were enrolled in the study and 87 subjects received study medication. Two subjects who did not receive study treatment were wrongly classified as enrolled by the sites.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Macitentan 10 mg

Arm description:

Subjects received macitentan 10 milligrams (mg) tablets once daily until the premature discontinuation of study drug or end of treatment (EOT) on the day of the last dose of study drug at Week 52.

Arm type	Experimental
Investigational medicinal product name	Macitentan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Macitentan 10 mg tablets once daily.

Number of subjects in period 1	Macitentan 10 mg
Started	87
Completed	72
Not completed	15
Adverse event, serious fatal	1
Consent withdrawn by subject	1
Lost to follow-up	1
Sponsor decision	12

Baseline characteristics

Reporting groups	
Reporting group title	Macitentan 10 mg
Reporting group description:	
Subjects received macitentan 10 milligrams (mg) tablets once daily until the premature discontinuation of study drug or end of treatment (EOT) on the day of the last dose of study drug at Week 52.	

Reporting group values	Macitentan 10 mg	Total	
Number of subjects	87	87	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	75	75	
From 65 to 74 years	12	12	
75 years and over	0	0	
Title for AgeContinuous Units: years			
arithmetic mean	45.9		
standard deviation	± 14.48	-	
Title for Gender Units: subjects			
Female	70	70	
Male	17	17	

End points

End points reporting groups

Reporting group title	Macitentan 10 mg

Reporting group description:

Subjects received macitentan 10 milligrams (mg) tablets once daily until the premature discontinuation of study drug or end of treatment (EOT) on the day of the last dose of study drug at Week 52.

Primary: Change From Baseline in Right Ventricular Stroke Volume (RVSV) at Week 26

End point title	Change From Baseline in Right Ventricular Stroke Volume (RVSV) at Week 26[1]

End point description:

Change from baseline in RVSV assessed by cardiac magnetic resonance imaging (MRI) from pulmonary artery flow was reported at Week 26. The primary analysis was based on interim results as pre-planned and the primary outcome measures data table reported is finalized as is. The Modified full analysis set (mFAS) included all screened subjects who received at least one dose of the study drug and who had a baseline as well as a post-baseline measurement taken between 16 weeks and 30 weeks of treatment.

End point type	Primary

End point timeframe:

Baseline and Week 26

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Milliliters (mL)				
least squares mean (standard error)	15.17 (± 2.75)			

Statistical analyses

No statistical analyses for this end point

Primary: Ratio of Week 26 to Baseline Pulmonary Vascular Resistance (PVR)

End point title	Ratio of Week 26 to Baseline Pulmonary Vascular Resistance (PVR)[2]

End point description:

Ratio of Week 26 to baseline PVR as assessed by RHC was reported. PVR represents the resistance against which the right ventricle needs to pump. PVR is determined by right heart catheterization (RHC). PVR was calculated as 80*(Mean pulmonary arterial pressure [mPAP] –[Pulmonary capillary wedge pressure {PCWP} or Left ventricular end diastolic pressure {LVEDP} if PCWP not available/cardiac output [CO]). The primary analysis was based on interim results as pre-planned and the primary outcome measures data table reported is finalized as is. mFAS included all screened subjects who received at least one dose of study drug and who had a baseline as well as a post-baseline measurement taken between 16 weeks and 30 weeks of treatment.

End point type	Primary

End point timeframe:

Baseline and Week 26

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Ratio				
geometric mean (geometric coefficient of variation)	0.63 (± 0.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Right Ventricular End Diastolic Volume (RVEDV) to Week 26

End point title	Change From Baseline in Right Ventricular End Diastolic Volume (RVEDV) to Week 26

End point description:

Change from baseline to Week 26 in RVEDV assessed by cardiac MRI was reported. Safety set included all screened subjects who received at least one dose of study drug. Here 'N' (number of subjects analyzed) signifies the number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 26

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: mL				
least squares mean (confidence interval 95%)	-6.22 (-12.50 to 0.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Right Ventricular End Systolic Volume (RVESV) to Week 26

End point title	Change From Baseline in Right Ventricular End Systolic Volume (RVESV) to Week 26

End point description:

Change from baseline to Week 26 in RVESV assessed by cardiac MRI was reported. Safety set included all screened subjects who received at least one dose of study drug. Here 'N' (number of subjects analyzed) signifies the number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: mL				
least squares mean (confidence interval 95%)	-16.39 (-20.56 to -12.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Right Ventricular Ejection Fraction (RVEF) to Week 26 (% Blood Volume)

End point title	Change From Baseline in Right Ventricular Ejection Fraction (RVEF) to Week 26 (% Blood Volume)

End point description:

Change from baseline to Week 26 in RVEF based on pulmonary artery flow assessed by cardiac MRI was reported. Safety set included all screened subjects who received at least one dose of study drug. Here 'N' (number of subjects analyzed) signifies the number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Percentage of blood volume				
least squares mean (confidence interval 95%)	10.14 (7.46 to 12.83)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Right Ventricle (RV) Mass to Week 26

End point title	Change From Baseline in Right Ventricle (RV) Mass to Week 26

End point description:

Change from baseline to Week 26 in RV mass assessed by cardiac MRI was reported. Safety set included all screened subjects who received at least one dose of study drug. Here 'N' (number of subjects analyzed) signifies the number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 26

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: Gram				
least squares mean (confidence interval 95%)	-10.10 (-13.81 to -6.39)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Six Minutes Walk Distance (6MWD) to Week 26

End point title	Change From Baseline in Six Minutes Walk Distance (6MWD) to Week 26

End point description:

6MWD is a non-encouraged test performed in a 30 meter (m) long flat corridor, where the subject is instructed to walk as far as possible, back and forth around two cones, with the permission to slow down, rest, or stop if needed. This test is used to assess exercise capacity. The test was performed about 30 minutes after study drug administration. Any increase in the walk distance was considered improvement from baseline. Safety Set included all screened subjects who received at least one dose of study drug. Here 'N' (number of subjects analyzed) signifies the number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 26

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	83			
Units: Meters				
least squares mean (standard error)	38.85 (± 7.37)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in World Health Organization Functional Class (WHO FC) to Week 26

End point title	Change From Baseline in World Health Organization Functional Class (WHO FC) to Week 26

End point description:

WHO FC is a classification which reflects disease severity based on symptoms. WHO Functional Classification of pulmonary hypertension comprises of Class I (subjects with pulmonary hypertension but without resulting limitation of physical activity), II (subjects with pulmonary hypertension resulting in slight limitation of physical activity), III (subjects with pulmonary hypertension resulting in marked limitation of physical activity) and IV (subjects with pulmonary hypertension with inability to carry out any physical activity without symptoms). Changes from baseline to Week 26 included: improvement (change from a higher to a lower FC), worsening (change from a lower to a higher FC) or unchanged/stable (same FC at baseline and at the post-baseline time point). Safety Set included all screened subjects who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline to Week 26

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	87			
Units: Subjects				
number (not applicable)				
Missing WHO FC	5			
Worsened WHO FC	1			
Unchanged WHO FC	35			
Improved WHO FC	46			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 420 Days

Adverse event reporting additional description:

Safety Set included all screened subjects who received at least one dose of study drug.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Macitentan 10 mg

Reporting group description:

Subjects received macitentan 10 milligrams (mg) tablets once daily until the premature discontinuation of study drug or end of treatment (EOT) on the day of the last dose of study drug at Week 52.

Serious adverse events	Macitentan 10 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 87 (17.24%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic Carcinoma			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Therapeutic Response Decreased			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			

Dysfunctional Uterine Bleeding				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysmenorrhoea				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Menorrhagia				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pelvic Haemorrhage				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary Arterial Hypertension				
subjects affected / exposed	2 / 87 (2.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary Embolism				
subjects affected / exposed	2 / 87 (2.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	2 / 87 (2.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Angina Pectoris			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial Fibrillation			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac Arrest			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Coronary Artery Disease			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Right Ventricular Failure			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular Hypokinesia			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemolytic Anaemia			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Iron Deficiency Anaemia			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Rectal Haemorrhage			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Rheumatoid Arthritis			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Systemic Lupus Erythematosus			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cholangitis Infective			

subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cytomegalovirus Infection			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia Bacteraemia			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes Zoster			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	3 / 87 (3.45%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 87 (2.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Infection			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Macitentan 10 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 87 (65.52%)		
Investigations			
Haemoglobin Decreased			
subjects affected / exposed	10 / 87 (11.49%)		
occurrences (all)	11		
Vascular disorders			
Flushing			
subjects affected / exposed	5 / 87 (5.75%)		
occurrences (all)	5		
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 87 (13.79%)		
occurrences (all)	13		
Headache			
subjects affected / exposed	18 / 87 (20.69%)		
occurrences (all)	19		
General disorders and administration site conditions			
Oedema Peripheral			
subjects affected / exposed	19 / 87 (21.84%)		
occurrences (all)	19		
Pyrexia			
subjects affected / exposed	7 / 87 (8.05%)		
occurrences (all)	9		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 87 (9.20%)		
occurrences (all)	9		
Nausea			
subjects affected / exposed	6 / 87 (6.90%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all) Nasal Congestion subjects affected / exposed occurrences (all)	10 / 87 (11.49%) 10 8 / 87 (9.20%) 8		
Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in Extremity subjects affected / exposed occurrences (all)	7 / 87 (8.05%) 7 9 / 87 (10.34%) 11 6 / 87 (6.90%) 7		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	6 / 87 (6.90%) 7 10 / 87 (11.49%) 17		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 February 2015	This amendment included the following changes: initial combination therapy with macitentan and a PDE-5 inhibitor was allowed in treatment-naive participants; pressure-volume endpoints were to be analyzed as exploratory endpoints instead of secondary endpoints; MRI variables were removed from the metabolism substudy.
13 August 2015	This amendment included the following changes: RHC data obtained at the study site before informed consent signature were accepted if RHC was performed between Day −28 and Day 1; spirometry eligibility criteria were simplified.
30 May 2016	This amendment included the following changes: eligibility criteria were modified to include participants with PAH associated with connective tissue disease, elderly participants up to 74 years of age, and subjects with a cMRI-compatible pacemaker; the window to perform cMRI and RHC within 7 days of each other was extended to 21 days.
08 November 2016	This amendment included the following change: an interim analysis for efficacy was added to the protocol to allow for study termination if both primary endpoints were met early.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported