Clinical trial results:
Prospective, Multicenter, Open-label Study Evaluating the Effects of First-line Oral Combination Therapy of Macitentan and Tadalafil in Patients with Newly Diagnosed Pulmonary Arterial Hypertension

Summary

EudraCT number	2015-002078-19
Trial protocol	FR
Global end of trial date	10 September 2018

Results information

Result version number	v1 (current)
This version publication date	21 September 2019
First version publication date	21 September 2019

Trial information

Trial identification

Sponsor protocol code	AC-055-405

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02968901
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals
Sponsor organisation address	21 Boulevard De La Madeleine, Paris, France, 75001
Public contact	Clinical Registry Group, Actelion Pharmaceuticals, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Actelion Pharmaceuticals, ClinicalTrialsEU@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	Final
Date of interim/final analysis	10 September 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 September 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to document the effect of first line dual oral combination therapy with macitentan 10 milligram (mg) and tadalafil 40 mg on pulmonary vascular resistance (PVR) in treatment-naïve subjects with newly diagnosed 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 evaluations included monitoring of adverse events (AEs), serious adverse events (SAEs), clinical laboratory parameters (liver function tests [LFTs], creatinine, hemoglobin and biomarkers of myocardial stress), vital signs, electrocardiograms (ECG), weight, height and physical examination.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 November 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	France: 46
Worldwide total number of subjects	46
EEA total number of subjects	46

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)	25
From 65 to 84 years	21

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 46 subjects were enrolled and treated with macitentan and tadalafil. Of these, 2 subjects discontinued the study and 44 subjects entered the extension period of whom 39 subjects completed this OPTIMA study and were enrolled into the UMBRELLA (AC-055-314 [NCT03422328]) study.

Period 1

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

Arms

Arm title	Macitentan 10 mg / Tadalafil 40 mg

Arm description:

Subjects received macitentan 10 mg film-coated tablets and tadalafil 40 mg (2*20 mg) tablets administered orally once daily starting on Day 1 of Open-label period up to Day 15. Subject were then continued to Maintenence treatment period (Day 15 to End of treatment 1 [EOT1]) and then to Extension period (EOT1 to End of treatment 2 (EOT2). EOT1, defined as the earliest of the followings: a. Visit 3 at Week 16 ± 1 week; b. Pulmonary arterial hypertension (PAH) progression requiring intake of other PAH-specific drug(s); c. Sponsor decision to stop the trial;d. Subject or investigator decision to discontinue both study treatments. EOT2, defined as the earliest time at which one of the following occurred: a. Commercial availability and reimbursement of macitentan in France; b. Sponsor decision to stop the trial; c. Subject or investigator decision to discontinue both study treatments.

Arm type	Experimental
Investigational medicinal product name	Macitentan 10 mg
Investigational medicinal product code	
Other name	Opsumit®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received macitentan 10 mg once daily.

Investigational medicinal product name	Tadalafil 40 mg
Investigational medicinal product code	
Other name	Adcirca®)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received tadalafil 40 mg once daily.

Number of subjects in period 1	Macitentan 10 mg / Tadalafil 40 mg
Started	46
Completed	39
Not completed	7
Adverse event, serious fatal	3

Physician decision	2
Consent withdrawn by subject	1
Sponsor decision	1

Baseline characteristics

Reporting groups	
Reporting group title	Macitentan 10 mg / Tadalafil 40 mg

Reporting group description:

Subjects received macitentan 10 mg film-coated tablets and tadalafil 40 mg (2*20 mg) tablets administered orally once daily starting on Day 1 of Open-label period up to Day 15. Subject were then continued to Maintenence treatment period (Day 15 to End of treatment 1 [EOT1]) and then to Extension period (EOT1 to End of treatment 2 (EOT2). EOT1, defined as the earliest of the followings: a. Visit 3 at Week 16 ± 1 week; b. Pulmonary arterial hypertension (PAH) progression requiring intake of other PAH-specific drug(s); c. Sponsor decision to stop the trial;d. Subject or investigator decision to discontinue both study treatments. EOT2, defined as the earliest time at which one of the following occurred: a. Commercial availability and reimbursement of macitentan in France; b. Sponsor decision to stop the trial; c. Subject or investigator decision to discontinue both study treatments.

Reporting group values	Macitentan 10 mg / Tadalafil 40 mg	Total	
Number of subjects	46	46	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	25	25	
From 65 to 84 years	21	21	
85 years and over	0	0	
Title for AgeContinuous Units: years			
arithmetic mean	57.4		
standard deviation	± 14.89	-	
Title for Gender Units: subjects			
Female	30	30	
Male	16	16	

End points

End points reporting groups

Reporting group title	Macitentan 10 mg / Tadalafil 40 mg

Reporting group description:

Subjects received macitentan 10 mg film-coated tablets and tadalafil 40 mg (2*20 mg) tablets administered orally once daily starting on Day 1 of Open-label period up to Day 15. Subject were then continued to Maintenence treatment period (Day 15 to End of treatment 1 [EOT1]) and then to Extension period (EOT1 to End of treatment 2 (EOT2). EOT1, defined as the earliest of the followings: a. Visit 3 at Week 16 ± 1 week; b. Pulmonary arterial hypertension (PAH) progression requiring intake of other PAH-specific drug(s); c. Sponsor decision to stop the trial;d. Subject or investigator decision to discontinue both study treatments. EOT2, defined as the earliest time at which one of the following occurred: a. Commercial availability and reimbursement of macitentan in France; b. Sponsor decision to stop the trial; c. Subject or investigator decision to discontinue both study treatments.

Primary: Pulmonary Vascular Resistance (PVR) Ratio between Baseline and Week 16 as Assessed by Right Heart Catheterization (RHC)

End point title	Pulmonary Vascular Resistance (PVR) Ratio between Baseline and Week 16 as Assessed by Right Heart Catheterization (RHC)[1]

End point description:

PVR was calculated and assessed by RHC. PVR [dyn.sec/cm−5] was calculated as mPAP-PCWP/CO*80 (If PCWP was missing, LVEDP was used instead). Here, mPAP, PCWP, CO and LVEDP means Mean pulmonary arterial pressure, Pulmonary capillary wedge pressure, Cardiac output and Left ventricular end-diastolic pressure respectively. A geometric mean ratio of Week 16 to baseline <1 corresponded to an improvement (reduction in PVR from baseline). The Haemodynamic Set included all subjects from the safety set who had a baseline PVR measurement.

End point type	Primary

End point timeframe:

Baseline and Week 16

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 / Tadalafil 40 mg			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: Ratio				
geometric mean (confidence interval 95%)	0.53 (0.47 to 0.59)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Clinically Meaningful Improvement in PVR at Week 16 (decrease of >=30 Percent [%] from Baseline to Week 16)

End point title	Percentage of Subjects with Clinically Meaningful Improvement in PVR at Week 16 (decrease of >=30 Percent [%] from

	Baseline to Week 16)

End point description:

Percentage of subjects with clinically meaningful improvement in PVR at Week 16 (decrease of >=30% from baseline to Week 16) were reported. The Haemodynamic Set included all subjects from the safety set who had a baseline PVR measurement.

End point type	Secondary

End point timeframe:

Week 16

End point values	Macitentan 10 mg / Tadalafil 40 mg			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: Percentage of subjects				
number (confidence interval 95%)	86.96 (73.74 to 95.06)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 16 in Mean Right Atrial Pressure (mRAP)

End point title	Change from Baseline to Week 16 in Mean Right Atrial Pressure (mRAP)

End point description:

Change from baseline to Week 16 in mRAP was reported. mRAP is the mean blood pressure in the right atrium of the heart. The Haemodynamic Set included all subjects from the safety set who had a baseline PVR measurement.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Macitentan 10 mg / Tadalafil 40 mg			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)	-0.28 (± 5.56)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 16 in Mean Pulmonary Arterial Pressure (mPAP)

End point title	Change from Baseline to Week 16 in Mean Pulmonary Arterial Pressure (mPAP)

End point description:

Change from baseline to Week 16 in mean pulmonary arterial pressure (mPAP) was reported. mPAP is the mean blood pressure inside the pulmonary artery which moves the blood from the heart to the lungs. Monitoring of mPAP can detect small changes in the function of the heart. The Haemodynamic Set included all subjects from the safety set who had a baseline PVR measurement.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Macitentan 10 mg / Tadalafil 40 mg			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: mmHg				
arithmetic mean (standard deviation)	-7.83 (± 13.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 16 in Cardiac Index (CI)

End point title	Change from Baseline to Week 16 in Cardiac Index (CI)

End point description:

Change from Baseline to Week 16 in cardiac index (CI) was reported. The cardiac index is an assessment of the function of the heart and relates the cardiac output to the subject's body size (the patient's body surface area). The Haemodynamic Set included all subjects from the safety set who had a baseline PVR measurement.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Macitentan 10 mg / Tadalafil 40 mg			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: Liter per minute per meter^2 (L/min/m^2)				
arithmetic mean (standard deviation)	0.91 (± 0.66)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 16 in Total Pulmonary Resistance (TPR)

End point title	Change from Baseline to Week 16 in Total Pulmonary Resistance (TPR)

End point description:

Change from Baseline to Week 16 in total pulmonary resistance (TPR) was reported. TPR is the resistance the pulmonary circulation that must be overcome in order for the blood flow to occur. It takes into account the blood pressure in the pulmonary arteries and the cardiac output. It is an important measurement to monitor the function of the pulmonary circulation and detect disease progression or improvement. The Haemodynamic Set included all subjects from the safety set who had a baseline PVR measurement.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Macitentan 10 mg / Tadalafil 40 mg			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: dyn*sec/cm^−5				
arithmetic mean (standard deviation)	-431.97 (± 308.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 16 in Mixed Venous Oxygen Saturation (SvO2)

End point title	Change from Baseline to Week 16 in Mixed Venous Oxygen Saturation (SvO2)

End point description:

Change from baseline to Week 16 in mixed venous oxygen saturation (SvO2) was reported. SVO2 help assess tissue oxygen delivery. It describes the percentage of oxygen bound to hemoglobin in the blood which returns to the heart. This reflects the amount of residual oxygen in the blood after oxygen extraction by the tissues throughout the body. The Haemodynamic Set included all subjects from the safety set who had a baseline PVR measurement. Here 'N' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Macitentan 10 mg / Tadalafil 40 mg			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Percentage of Oxygen saturation				
arithmetic mean (standard deviation)	5.53 (± 7.19)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 16 in 6-Minute Walk Distance (6MWD)

End point title	Change from Baseline to Week 16 in 6-Minute Walk Distance (6MWD)

End point description:

Change from baseline to Week 16 in 6-minute walk distance (6MWD) was reported. 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. The Haemodynamic Set included all subjects from the safety set who had a baseline PVR measurement.

End point type	Secondary

End point timeframe:

Week 16

End point values	Macitentan 10 mg / Tadalafil 40 mg			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: Meters				
arithmetic mean (standard deviation)	35.8 (± 67.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 16 in World Health Organization Functional Class (WHO-FC) (Change from WHO-FC III to WHO-FC I, from WHO-FC III to WHO-FC II, and WHO-FC II to WHO-FC I)

End point title	Change from Baseline to Week 16 in World Health Organization

	Functional Class (WHO-FC) (Change from WHO-FC III to WHO-FC I, from WHO-FC III to WHO-FC II, and WHO-FC II to WHO-FC I)

End point description:

Changes from baseline to Week 16 in WHO FC were dichotomized as worsening (that is, change > 0) versus no change or improvement (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 (example. 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 (example. dyspnea and/or fatigue) and inability to carry out any physical activity without symptoms. Subjects in class IV manifest signs of right heart failure. The Haemodynamic Set included all subjects from the safety set who had a baseline PVR measurement. Here 'N' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Macitentan 10 mg / Tadalafil 40 mg			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Percentage of subjects				
number (not applicable)				
Change at Week 16: WHO-FC III to WHO-FC I	5.56			
Change at Week 16: WHO-FC III to WHO-FC II	55.56			
Change at Week 16: WHO-FC II to WHO-FC I	70.00			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Improvement or Worsening of WHO-FC from Baseline to Week 16

End point title	Percentage of Subjects with Improvement or Worsening of WHO-FC from Baseline to Week 16

End point description:

Percentage of subjects with improvement/worsening of WHO-FC from Baseline to Week 16 were reported. WHO FC were dichotomized as worsening (that is, change > 0) versus no change or improvement (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 (example. 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 (example. dyspnea and/or fatigue) and inability to carry out any physical activity without symptoms. Subjects in class IV manifest signs of right heart failure. The Haemodynamic Set included all subjects from the safety set who had a baseline PVR measurement. Here 'N' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 16

End point values	Macitentan 10 mg / Tadalafil 40 mg			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Percentage of subjects				
number (not applicable)				
Week 16: Subjects with Improvement in WHO-FC	63.04			
Week 16: Subjects with Worsening in WHO-FC	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 16 in N-terminal pro B-type Natriuretic Peptide (NT-proBNP)

End point title	Change from Baseline to Week 16 in N-terminal pro B-type Natriuretic Peptide (NT-proBNP)

End point description:

Change from baseline to Week 16 in NT-proBNP was reported. The Haemodynamic Set included all subjects from the safety set who had a baseline PVR measurement. Here 'N' (number of subjects analysed) signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Macitentan 10 mg / Tadalafil 40 mg			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: Nanogram per Litre (ng/L)				
arithmetic mean (standard deviation)	-1086.5 (± 2004.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 34 months

Adverse event reporting additional description:

Safety analysis set included all subjects who received at least one dose of any of the two study treatments.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Macitentan 10 mg / Tadalafil 40 mg

Reporting group description:

Subjects received macitentan 10 mg and tadalafil 40 mg once daily.

Serious adverse events	Macitentan 10 mg / Tadalafil 40 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 46 (28.26%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoma			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary Hypertension			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Venoocclusive Disease			

subjects affected / exposed	2 / 46 (4.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Therapy Change			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest Pain			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug Effect Incomplete			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug Ineffective			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple Organ Dysfunction Syndrome			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Oedema Peripheral			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		

Pyrexia				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Treatment Failure				
subjects affected / exposed	1 / 46 (2.17%)			
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	3 / 46 (6.52%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Dyspnoea Exertional				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural Effusion				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary Arterial Hypertension				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Product issues				
Device Breakage				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Investigations			
White Blood Cell Count Increased			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Head Injury			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arteriosclerosis Coronary Artery			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac Arrest			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 1		
Cardiac Failure			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Hepatojugular Reflux			

subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Left Ventricular Failure			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Right Ventricular Failure			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	1 / 1		
Nervous system disorders			
Presyncope			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic Pain			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			

subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory Tract Infection			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal Bacteraemia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Fluid Retention			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Macitentan 10 mg / Tadalafil 40 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 46 (76.09%)		
Investigations			
Weight Decreased			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Cardiac disorders			
Palpitations			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	4		
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 46 (8.70%)		
occurrences (all)	4		
Headache			

subjects affected / exposed	11 / 46 (23.91%)		
occurrences (all)	15		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 46 (10.87%)		
occurrences (all)	6		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 46 (10.87%)		
occurrences (all)	6		
Face Oedema			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Influenza Like Illness			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Oedema Peripheral			
subjects affected / exposed	11 / 46 (23.91%)		
occurrences (all)	13		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 46 (19.57%)		
occurrences (all)	11		
Nausea			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 46 (10.87%)		
occurrences (all)	5		
Dyspnoea			
subjects affected / exposed	5 / 46 (10.87%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all) Back Pain subjects affected / exposed occurrences (all) Pain in Extremity subjects affected / exposed occurrences (all)	3 / 46 (6.52%) 4 4 / 46 (8.70%) 6 4 / 46 (8.70%) 5		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 46 (6.52%) 3 3 / 46 (6.52%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 October 2015	The overall reason for global amendment 1 was to clarify the eligibility criterias. Inclusion criterion 6 was clarified: only congenital heart disease corrected with simple systemic-to-pulmonary shunt (atrial septal defect, ventricular septal defect, patent ductus arteriosus), with persistent PAH >= 1 year after surgical repair.
29 March 2016	The overall reason for the amendment was to clarify the eligibility criteria and include new committee. An adjudication committee has been set up to determine if a subject can be included despite of a Diffusing capacity of the lung for carbon monoxide (DLCO) greater than (<) 40 percentage (%). Exclusion criterion 2 was changed: Subjects who changed the dose or discontinued calcium channel blockers within 1 week prior to Day 1. Exclusion criterion 9 was clarified: Significant aortic and mitral valve disease treated with a specific treatment. Exclusion criterion 11 (Significant left ventricular dysfunction in the opinion of the investigator) was deleted. Exclusion criterion 20 was created [DLCO < 40% of predicted value (eligible only if no sign of enoocclusive disease according to adjudication committee]. DLCO < 40% of predicted value was deleted from Exclusion criteria 21. Calcium channel blocker were authorized if present at a stable dose for at least 1 week before Day 1 instead of 3 months. Assessment of NT-proBNP were changed: Laboratory assessment were done on blood samples collected at inclusion visit and at Week 16. Finally, laboratory tests for screening and Day 1 can be performed on the same day.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was stopped early due to a slow recruitment rate.

Notes: