Clinical trial results:
AC-055-311 (ORCHESTRA Extension) An extension of AC-055-310, ORCHESTRA, a Prospective, Multi-center, Open-label, Single-arm, Phase 3b Extension Study of Macitentan in Subjects With PAH to Assess the Long-term Safety of Macitentan

Summary

EudraCT number	2013-003489-15
Trial protocol	IT ES
Global end of trial date	17 September 2018

Results information

Result version number	v1 (current)
This version publication date	05 September 2019
First version publication date	05 September 2019

Trial information

Trial identification

Sponsor protocol code	AC-055-311

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02112487
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, 4123
Public contact	Actelion Pharmaceuticals Ltd, Actelion Pharmaceuticals Ltd, aziar.assadi-gehr@actelion.com
Scientific contact	Actelion Pharmaceuticals Ltd, Actelion Pharmaceuticals Ltd, aziar.assadi-gehr@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	17 September 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study was to assess the long-term safety of macitentan in subjects with pulmonary arterial hypertension (PAH).

Protection of trial subjects:

The sponsor and investigators ensured that the study was conducted in full compliance with the principles of the Declaration of Helsinki and with the laws and regulations of the country in which the research was conducted. Documentary evidence of adequate Good Clinical Practice (GCP) training of the investigator was collected. The safety assessments included evaluation of adverse events (AEs), clinical laboratory measurements, vital signs, physical findings and 12-lead electrocardiograms (ECGs).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 June 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	52 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	France: 43
Country: Number of subjects enrolled	Italy: 16
Worldwide total number of subjects	88
EEA total number of subjects	88

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)	59
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total 88 subjects were enrolled in AC-055-310 and 81 subjects completed the study. Out of them, 74 subjects were enrolled in extension Study AC-055-311 and 41 subjects completed both studies (i.e., stopped receiving study drug due to commercial availability and reimbursement of study drug), and 47 subjects prematurely discontinued either study.

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

Arm description:

Subjects received Macitentan 10 milligram (mg) film-coated tablets once daily orally for 16 weeks.

Arm type	Experimental
Investigational medicinal product name	Macitentan
Investigational medicinal product code	
Other name	ACT-064992
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Macitentan 10 milligram (mg) film-coated tablets once daily orally for 16 weeks.

Number of subjects in period 1	Macitentan
Started	88
Completed	41
Not completed	47
Adverse event, serious fatal	13
Physician decision	5
Consent withdrawn by subject	1
Unspecified	28

Baseline characteristics

Reporting groups	
Reporting group title	Macitentan
Reporting group description:	
Subjects received Macitentan 10 milligram (mg) film-coated tablets once daily orally for 16 weeks.	

Reporting group values	Macitentan	Total	
Number of subjects	88	88	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	59	59	
From 65 to 84 years	29	29	
85 years and over	0	0	
Title for AgeContinuous Units: years			
arithmetic mean	55.9		
standard deviation	± 13.37	-	
Title for Gender Units: subjects			
Female	58	58	
Male	30	30	

End points

End points reporting groups

Reporting group title	Macitentan

Reporting group description:

Subjects received Macitentan 10 milligram (mg) film-coated tablets once daily orally for 16 weeks.

Primary: Number of Subjects Reporting Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Subjects Reporting Treatment-Emergent Adverse Events (TEAEs)[1]

End point description:

An adverse event (AE) was any untoward medical occurrence in a subjectt who received study drug without regard to possibility of causal relationship. Treatment-emergent adverse event is defined as an event with the onset date on or after the study treatment start date (i.e., Study Day 1) and on or before 30 days after study drug discontinuation or initiation of commercial macitentan. The Safety set included all subjects who received at least 1 dose of study treatment in Study AC-055-310 regardless of whether they continued into Study AC-055-311.

End point type	Primary

End point timeframe:

Up to 4.3 years

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: No statistical analyses was planned for this specified endpoint.

End point values	Macitentan			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: Subjects	79			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Reporting Treatment-Emergent Serious Adverse Events (TESAEs)

End point title	Number of Subjects Reporting Treatment-Emergent Serious Adverse Events (TESAEs)[2]

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent adverse event is defined as an event with the onset date on or after the study treatment start date (i.e., Study Day 1) and on or before 30 days after study drug discontinuation or initiation of commercial macitentan. The Safety set included all subjects who received at least 1 dose of study treatment in Study AC-055-310 regardless of whether they continued into Study AC-055-311.

End point type	Primary

End point timeframe:

Up to 4.3 years

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: No statistical analyses was planned for this specified endpoint.

End point values	Macitentan			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: Subjects	44			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Treatment-emergent Alanine Aminotransferase (ALT) and/or Aminotransferase (AST) Abnormalities up to End of Treatment (EOT)

End point title	Percentage of Subjects with Treatment-emergent Alanine Aminotransferase (ALT) and/or Aminotransferase (AST) Abnormalities up to End of Treatment (EOT)[3]

End point description:

Percentage of subjects with treatment-emergent ALT and/or Aminotransferase (AST) abnormalities (greater than [>] 3*, > 5*, and > 8* upper limit of the normal range [ULN]) associated or not with total bilirubin > 2* ULN, up to EOT was reported. The Safety set included all subjects who received at least 1 dose of study treatment in Study AC-055-310 regardless of whether they continued into Study AC-055-311. Here, ALP indicates Alkaline phosphatase.

End point type	Primary

End point timeframe:

Up to 4.3 years

Notes:

[3] - 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: No statistical analyses was planned for this specified endpoint.

End point values	Macitentan			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: percentage of subjects				
number (not applicable)				
ALT > 3*ULN	1.1			
AST > 3*ULN	3.4			
ALT or AST > 3*ULN	3.4			
ALT or AST > 3*ULN, Bilirubin > 2*ULN, ALP =<2*ULN	0			
ALT > 3*ULN and <= 5*ULN	1.1			
ALT > 5*ULN and <= 8*ULN	0			
ALT > 8*ULN	0			
AST > 3*ULN and <= 5*ULN	3.4			
AST > 5*ULN and <= 8*ULN	0			
AST > 8*ULN	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Adverse Events Leading to Premature Discontinuation of Study Treatment

End point title	Number of Subjects with Adverse Events Leading to Premature Discontinuation of Study Treatment[4]

End point description:

Number of subjects with an adverse event that led to the permanent discontinuation of study treatment were reported. The Safety set included all subjects who received at least 1 dose of study treatment in Study AC-055-310 regardless of whether they continued into Study AC-055-311.

End point type	Primary

End point timeframe:

Up to 4.3 years

Notes:

[4] - 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: No statistical analyses was planned for this specified endpoint.

End point values	Macitentan			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: Subjects	15			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Hemoglobin Abnormalities up to EOT

End point title	Percentage of Subjects with Hemoglobin Abnormalities up to EOT[5]

End point description:

Percentage of subjects with hemoglobin abnormalities (less than or equal to <= 100 gram per liter (g/L) and >80g/L, and <= 80 g/L), up to EOT was reported. The Safety set included all subjects who received at least 1 dose of study treatment in Study AC-055-310 regardless of whether they continued into Study AC-055-311.

End point type	Primary

End point timeframe:

Up to 4.3 years

Notes:

[5] - 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: No statistical analyses was planned for this specified endpoint.

End point values	Macitentan			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: percentage of subjects				
number (not applicable)				
Hemoglobin <= 80g/L	2.3			
Hemoglolin > 80g/L and <= 100g/L	9.1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 4.3 years	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Macitentan
Reporting group description:	
Subjects received Macitentan 10 milligram (mg) film-coated tablets once daily orally for 16 weeks.	

Serious adverse events	Macitentan		
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 88 (50.00%)		
number of deaths (all causes)	13		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-Cell Lymphoma			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bladder Transitional Cell Carcinoma Recurrent			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast Cancer			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatocellular Carcinoma			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Langerhans' Cell Histiocytosis				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Leukaemia				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Lung Neoplasm				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous Cell Carcinoma				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Arterial Thrombosis				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arteriovenous Fistula				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Extremity Necrosis				
subjects affected / exposed	2 / 88 (2.27%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Haemorrhage				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral Ischaemia				

subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Shock Haemorrhagic				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Abortion Induced				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arterial Stent Insertion				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystectomy				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Finger Amputation				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Liver Ablation				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung Transplant				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sympathectomy				

subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest Discomfort			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest Pain			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Malaise			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema Peripheral			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	3 / 88 (3.41%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		

Cough				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	5 / 88 (5.68%)			
occurrences causally related to treatment / all	1 / 10			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	2 / 88 (2.27%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Interstitial Lung Disease				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary Arterial Hypertension				
subjects affected / exposed	8 / 88 (9.09%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 0			
Pulmonary Fibrosis				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary Oedema				

subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory Failure				
subjects affected / exposed	4 / 88 (4.55%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 1			
Product issues				
Device Material Issue				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Investigation				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Hip Fracture				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Toxicity to Various Agents				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute Right Ventricular Failure				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Angina Pectoris				

subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial Fibrillation				
subjects affected / exposed	2 / 88 (2.27%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Atrial Flutter				
subjects affected / exposed	2 / 88 (2.27%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Atrial Tachycardia				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac Arrest				
subjects affected / exposed	2 / 88 (2.27%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Cardiac Failure Congestive				
subjects affected / exposed	2 / 88 (2.27%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardio-Respiratory Arrest				
subjects affected / exposed	2 / 88 (2.27%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 2			
Coronary Artery Stenosis				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Right Ventricular Failure				

subjects affected / exposed	10 / 88 (11.36%)		
occurrences causally related to treatment / all	0 / 22		
deaths causally related to treatment / all	0 / 4		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Paraesthesia			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Transient Ischaemic Attack			
subjects affected / exposed	1 / 88 (1.14%)		
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 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile Neutropenia			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Iron Deficiency Anaemia			

subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Wall Haematoma			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal Hernia			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal Haemorrhage			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biliary Colic			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis Acute			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Skin Ulcer			
subjects affected / exposed	1 / 88 (1.14%)		
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 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic Kidney Disease				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal Failure				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthritis				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchitis				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device Related Infection				
subjects affected / exposed	2 / 88 (2.27%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Fallopian Tube Abscess				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes Zoster				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	4 / 88 (4.55%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Pneumonia Pneumococcal				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory Tract Infection				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic Shock				

subjects affected / exposed	2 / 88 (2.27%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 88 (1.14%)		
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		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 88 (72.73%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	7 / 88 (7.95%)		
occurrences (all)	10		
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 88 (7.95%)		
occurrences (all)	8		
Headache			
subjects affected / exposed	18 / 88 (20.45%)		
occurrences (all)	32		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 88 (10.23%)		
occurrences (all)	11		
Thrombocytopenia			
subjects affected / exposed	5 / 88 (5.68%)		
occurrences (all)	5		

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 88 (12.50%)		
occurrences (all)	15		
Oedema Peripheral			
subjects affected / exposed	19 / 88 (21.59%)		
occurrences (all)	28		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	14 / 88 (15.91%)		
occurrences (all)	17		
Nausea			
subjects affected / exposed	5 / 88 (5.68%)		
occurrences (all)	6		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 88 (6.82%)		
occurrences (all)	9		
Dyspnoea			
subjects affected / exposed	15 / 88 (17.05%)		
occurrences (all)	18		
Epistaxis			
subjects affected / exposed	9 / 88 (10.23%)		
occurrences (all)	13		
Pulmonary Arterial Hypertension			
subjects affected / exposed	13 / 88 (14.77%)		
occurrences (all)	14		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 88 (7.95%)		
occurrences (all)	8		
Back Pain			
subjects affected / exposed	5 / 88 (5.68%)		
occurrences (all)	10		
Pain in Extremity			

subjects affected / exposed	8 / 88 (9.09%)		
occurrences (all)	11		
Pain in Jaw			
subjects affected / exposed	6 / 88 (6.82%)		
occurrences (all)	6		
Infections and infestations			
Bronchitis			
subjects affected / exposed	13 / 88 (14.77%)		
occurrences (all)	20		
Influenza			
subjects affected / exposed	5 / 88 (5.68%)		
occurrences (all)	5		
Nasopharyngitis			
subjects affected / exposed	5 / 88 (5.68%)		
occurrences (all)	13		
Respiratory Tract Infection			
subjects affected / exposed	5 / 88 (5.68%)		
occurrences (all)	5		
Rhinitis			
subjects affected / exposed	6 / 88 (6.82%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2014	The rationale of this global amendment throughout the protocol is that PAH-SYMPACTTM was to be replaced with PAH-SYMPACT®, indicating that it is a registered trademark in the countries participating in this study (France, Italy, Spain).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported