Clinical trial results:
AC-055-310/ORCHESTRA: A pulmOnary aRterial hypertension study with maCitentan to validate tHE PAH-SYMPACT® in FRAnce, Italy, and Spain
A multi-center, open-label, single-arm, Phase 3b study of macitentan in patients with pulmonary arterial hypertension to psychometrically validate the French, Italian, and Spanish versions of the PAH-SYMPACT®

Summary

EudraCT number	2013-003462-14
Trial protocol	IT ES
Global end of trial date	09 September 2015

Results information

Result version number	v1 (current)
This version publication date	07 May 2017
First version publication date	07 May 2017

Trial information

Trial identification

Sponsor protocol code	AC-055-310

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02081690
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ACTELION Pharmaceuticals Ltd.
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, 4123
Public contact	Laurie Bertrand, ACTELION Pharmaceuticals Ltd., 41 61 565 83 36,
Scientific contact	Laurie Bertrand, ACTELION Pharmaceuticals Ltd., 41 61 565 83 36,

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	09 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 September 2015
Global end of trial reached?	Yes
Global end of trial date	09 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the psychometric characteristics of reliability and construct validity of the French, Italian, and Spanish versions of the PAH-SYMPACT®

Protection of trial subjects:

The protocol and any material provided to the patient (such as a patient information sheet or description of the study used to obtain informed consent) were reviewed and approved by the appropriate Independent Ethics Committee (IEC) or Institutional Review Board (IRB), i.e., a review panel that was responsible for ensuring the protection of the rights, safety and well-being of the study subjects.
Actelion 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. GCP training was provided to investigators and investigational site staff. 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 subjects' 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.

Background therapy:

Concomitant treatment with oral diuretics was allowed if patients had been on a stable dose for at least 1 week prior to Baseline period and up to the Treatment Initiation visit. The following treatments for PAH were allowed if patients had been on a stable dose for at least 3 months before the Treatment Initiation visit:
• Oral PDE-5 inhibitors;
• Inhaled prostacyclin analogs;
• Calcium channel blockers.

Forbidden concomitant therapy included:
• ERAs, i.v. or s.c. prostanoids, and soluble guanylate cyclase stimulator unless initiated for clinical worsening of PAH;
• Strong CYP3A4 inducers;
• Any investigational drug.

Evidence for comparator: -

Actual start date of recruitment	27 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 42
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Spain: 29

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:

The study was conducted in 3 countries (France, Italy, and Spain), with patients enrolled in 37 centers.

Pre-assignment

Screening details:

The screening period lasted from Day −28 to Day −15 and included the Screening Visit (Visit 1).

Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Baseline period

Arm description:

Baseline period

Arm type	No IMP
Investigational medicinal product name	No IMP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Other use

Dosage and administration details:

No IMP

Number of subjects in period 1	Baseline period
Started	88
Completed	88

Period 2

Period 2 title	Macitentan treatment period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Macitentan
Arm description: Macitentan 10 mg o.d.	
Arm type	Experimental
Investigational medicinal product name	Macitentan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Macitentan 10 mg o.d. for 16 weeks

Number of subjects in period 2	Macitentan
Started	88
Completed	81
Not completed	7
Adverse event, serious fatal	3
Physician decision	3
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Baseline period
Reporting group description:	
Baseline period	

Reporting group values	Baseline period	Total	
Number of subjects	88	88	
Age categorical Units: Subjects			
Adults (18-64 years)	59	59	
From 65-84 years	29	29	
Age continuous Units: years			
median	57.5		
full range (min-max)	21 to 79	-	
Gender categorical Units:			
Male	30	30	
Female	58	58	

Subject analysis sets	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set (FAS) included all enrolled patients.	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Set (SS) included all patients who received at least one dose of study treatment, based on the actual treatment received	
Subject analysis set title	Validation Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description:	
Validation Analysis Set (VAS) comprised data from all patients included in the FAS who had no protocol deviation(s) that could affect the analysis.	
Subject analysis set title	Per-protocol Set
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per-protocol Set (PPS) comprised data from all patients included in the FAS who did not have any of the following protocol deviations: • Patients who did not receive study treatment • Patients who violated selected inclusion/exclusion criteria • Patients who received a prohibited concomitant PAH medication	

Reporting group values	Full Analysis Set	Safety Set	Validation Analysis Set
Number of subjects	88	88	87
Age categorical Units: Subjects			
Adults (18-64 years)	59		
From 65-84 years	29		
Age continuous Units: years			
median	57.5		
full range (min-max)	21 to 79		
Gender categorical Units:			
Male	30		
Female	58		

Reporting group values	Per-protocol Set		
Number of subjects	81		
Age categorical Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
Age continuous Units: years			
median	57.5		
full range (min-max)	21 to 79		
Gender categorical Units:			
Male	30		
Female	58		

End points

End points reporting groups

Reporting group title	Baseline period
Reporting group description: Baseline period	
Reporting group title	Macitentan
Reporting group description: Macitentan 10 mg o.d.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: The Full Analysis Set (FAS) included all enrolled patients.	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: The Safety Set (SS) included all patients who received at least one dose of study treatment, based on the actual treatment received	
Subject analysis set title	Validation Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description: Validation Analysis Set (VAS) comprised data from all patients included in the FAS who had no protocol deviation(s) that could affect the analysis.	
Subject analysis set title	Per-protocol Set
Subject analysis set type	Per protocol
Subject analysis set description: The Per-protocol Set (PPS) comprised data from all patients included in the FAS who did not have any of the following protocol deviations: • Patients who did not receive study treatment • Patients who violated selected inclusion/exclusion criteria • Patients who received a prohibited concomitant PAH medication	

Primary: Psychometric validation of the French, Italian and Spanish versions of the PAH-SYMPACT™ patient-reported outcome tool

End point title	Psychometric validation of the French, Italian and Spanish versions of the PAH-SYMPACT™ patient-reported outcome tool[1]
End point description: Evaluation of the psychometric characteristics of reliability and construct validity of the PAH-SYMPACT, and the ability of the PAH-SYMPACT to detect change.	
End point type	Primary
End point timeframe: From Screening Visit (Visit 1) to End of Treatment (EOT) Visit (Visit 4, 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: Not applicable due to specific study design

End point values	Macitentan	Validation Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	87	87		
Units: Not applicable (Score)				
arithmetic mean (standard deviation)				
MLFQ total score at Baseline	35 (± 20.8)	35 (± 20.8)		
MLFQ total score at Week 16	33.4 (± 23)	33.4 (± 23)		
Physical Dimension score at Baseline	16.9 (± 10)	16.9 (± 10)		
Physical Dimension score at Week 16	15.7 (± 10)	15.7 (± 10)		
Emotional Dimension score at Baseline	7.7 (± 6.6)	7.7 (± 6.6)		
Emotional Dimension score at Week 16	7.5 (± 7.2)	7.5 (± 7.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Change in the PAH-SYMPACT symptom and impact scores assessed by Clinician Global Impression of Change (CGI-C)

End point title	Change in the PAH-SYMPACT symptom and impact scores assessed by Clinician Global Impression of Change (CGI-C)

End point description:

Change in the PAH-SYMPACT symptom and impact scores assessed by the PAH-SYMPACT questionnaire - Clinician Global Impression of Change (CGI-C)

End point type	Primary

End point timeframe:

From Baseline Visit (Visit 2, Day 1) to Week 16

End point values	Macitentan	Per-protocol Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	87	87		
Units: Not applicable (Score)				
least squares mean (standard error)				
Cardiopulmonary symptoms_Responders	-0.08 (± 0.04)	-0.08 (± 0.04)		
Cardiopulmonary symptoms_No change	0.13 (± 0.1)	0.13 (± 0.1)		
Cardiopulmonary symptoms_Non-Responders	0.6 (± 0.16)	0.6 (± 0.16)		
Cardiovascular symptoms_Responders	-0.04 (± 0.05)	-0.04 (± 0.05)		
Cardiovascular symptoms_No change	0.02 (± 0.1)	0.02 (± 0.1)		
Cardiovascular symptoms_Non-Responders	0.16 (± 0.16)	0.16 (± 0.16)		
Physical impacts_Responders	-0.04 (± 0.05)	-0.04 (± 0.05)		
Physical impacts_No change	0.19 (± 0.19)	0.19 (± 0.05)		
Physical impacts_Non-Responders	0.83 (± 0.25)	0.83 (± 0.25)		
Cognitive/Emotional impacts_Responders	0.08 (± 0.09)	0.08 (± 0.09)		
Cognitive/Emotional impacts_No change	-0.28 (± 0.19)	-0.28 (± 0.19)		

Cognitive/Emotional impacts_Non-Responders	0.3 (± 0.26)	0.3 (± 0.26)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Not applicable	
Comparison groups	Macitentan v Per-protocol Set
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0 [3]
Method	Not applicable

Notes:

[2] - Not applicable

[3] - Not applicable

Primary: Change in the PAH-SYMPACT symptom and impact scores assessed by Patient Global Assessment of Disease Severity (PGA-S)

End point title	Change in the PAH-SYMPACT symptom and impact scores assessed by Patient Global Assessment of Disease Severity (PGA-S)[4]
End point description:	
Mean change in the PAH-SYMPACT symptom and impact scores assessed by the PAH-SYMPACT questionnaire - Patient Global Assessment of Disease Severity (PGA-S)	
End point type	Primary
End point timeframe:	
From Baseline Visit (Visit 2, Day 1) to Week 16	

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: Not applicable due to specific study design

End point values	Macitentan	Per-protocol Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	75	75		
Units: Not applicable (Score)				
least squares mean (standard error)				
Cardiopulmonary symptoms_Decline (>=1)	0.08 (± 0.12)	0.08 (± 0.12)		
Cardiopulmonary symptoms_Stable (0)	0.02 (± 0.06)	0.02 (± 0.06)		
Cardiopulmonary symptoms_Improvement (= -1)	-0.17 (± 0.11)	-0.17 (± 0.11)		
Cardiopulmonary symptoms_Better Improvement (< -1)	-0.08 (± 0.15)	-0.08 (± 0.15)		
Cardiovascular symptoms_Decline (>=1)	0.03 (± 0.1)	0.03 (± 0.1)		
Cardiovascular symptoms_Stable (0)	-0.06 (± 0.05)	-0.06 (± 0.05)		
Cardiovascular symptoms_Improvement (= -1)	-0.01 (± 0.1)	-0.01 (± 0.1)		

Cardiovascular symptoms_Better Improvement (< -1)	-0.07 (± 0.13)	-0.07 (± 0.13)		
Physical impacts_Decline (>=1)	-0.06 (± 0.19)	-0.06 (± 0.19)		
Physical impacts_Stable (0)	0.02 (± 0.09)	0.02 (± 0.09)		
Physical impacts_Improvement (= -1)	-0.23 (± 0.18)	-0.23 (± 0.18)		
Physical impacts_Better Improvement (< -1)	-0.06 (± 0.26)	-0.06 (± 0.26)		
Cognitive/Emotional impacts_Decline (>=1)	0.11 (± 0.18)	0.11 (± 0.18)		
Cognitive/Emotional impacts_Stable (0)	-0.06 (± 0.09)	-0.06 (± 0.09)		
Cognitive/Emotional impacts_Improvement (= -1)	0.08 (± 0.17)	0.08 (± 0.17)		
Cognitive/Emot. impacts_Better Improvement (< -1)	-0.25 (± 0.24)	-0.25 (± 0.24)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From study treatment initiation up to 30 days after study treatment discontinuation	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18

Reporting groups	
Reporting group title	Macitentan
Reporting group description:	
Macitentan	

Serious adverse events	Macitentan		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 88 (14.77%)		
number of deaths (all causes)	3		
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 / 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		
Vascular disorders			
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		
Haemorrhage			

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			
Cardiac arrest			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
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	4 / 88 (4.55%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
Surgical and medical procedures			
Sympathectomy			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
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		
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			
Dyspnoea			
subjects affected / exposed	3 / 88 (3.41%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
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		
Renal and urinary disorders			
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			
Pneumonia			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
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		

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	21 / 88 (23.86%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	5 / 88 (5.68%)		
occurrences (all)	6		
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 88 (12.50%)		
occurrences (all)	12		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	8 / 88 (9.09%)		
occurrences (all)	8		

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