Clinical trial results:
A randomized, double-blind, placebo-controlled, prospective, multicenter, parallel group study to assess the safety and efficacy of macitentan in patients with portopulmonary hypertension

Summary

EudraCT number	2014-004624-21
Trial protocol	GB DE CZ ES FR
Global end of trial date	

Results information

Result version number	v1
This version publication date	09 November 2018
First version publication date	09 November 2018

Trial information

Trial identification

Sponsor protocol code	AC-055-404

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02382016
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ACTELION Pharmaceuticals Ltd.
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, 4123
Public contact	Clinical Trial Disclosure Desk, ACTELION Pharmaceuticals Ltd., clinical-trials-disclosure@its.jnj.com
Scientific contact	Clinical Trial Disclosure Desk, ACTELION Pharmaceuticals Ltd., clinical-trials-disclosure@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	Interim
Date of interim/final analysis	06 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 October 2017
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of macitentan on pulmonary vascular resistance (PVR) as compared to placebo in patients with portopulmonary hypertension (PoPH).

Protection of trial subjects:

Prior to the start of the study, each study site consulted an 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 human subjects involved in a clinical investigation. The study was conducted in compliance with the principles of the 'Declaration of Helsinki', the International Council for Harmonisation (ICH)-Good Clinical Practice (GCP) guidelines, and with the laws and regulations of the country in which the clinical research was conducted. Both Actelion and the investigator had the right to terminate the study at any time, and in such a case, were responsible for protecting the 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. A description of any incentives to participate in the study was provided in the informed consent form.

Background therapy:

As per randomization stratification, 63.5% of patients (54 out of 85 patients) were receiving a pulmonary arterial hypertension (PAH)-specific therapy at baseline.

Evidence for comparator: -

Actual start date of recruitment	23 June 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	Brazil: 5
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	France: 39
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 23
Worldwide total number of subjects	85
EEA total number of subjects	57

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)	64
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients at 39 sites in 7 countries were screened and were randomized at 36 sites in these 7 countries (Brazil, Czech Republic, France, Germany, Spain, UK and US).

Pre-assignment

Screening details:

A total of 119 patients were screened and off these, 85 patients at were randomized (43 to macitentan 10 mg once daily and 42 to matching placebo) and received double-blind (DB) study treatment. Overall, 80 patients who completed the DB treatment period entered the open-label treatment period.

Period 1

Period 1 title	DB treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Macitentan 10 mg

Arm description:

Macitentan 10 mg to be taken once daily, oral use, film-coated tablet

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

Dosage and administration details:

Macitentan 10 mg to be taken once daily

Arm title	Placebo

Arm description:

Macitentan-matching placebo to be taken once daily, oral use, film-coated tablet

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Macitentan-matching placebo to be taken once daily

Number of subjects in period 1	Macitentan 10 mg	Placebo
Started	43	42
Completed	39	41
Not completed	4	1
Physician decision	3	-
Consent withdrawn by subject	-	1
Lack of efficacy	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Macitentan 10 mg
Reporting group description:	
Macitentan 10 mg to be taken once daily, oral use, film-coated tablet	
Reporting group title	Placebo
Reporting group description:	
Macitentan-matching placebo to be taken once daily, oral use, film-coated tablet	

Reporting group values	Macitentan 10 mg	Placebo	Total
Number of subjects	43	42	85
Age categorical Units: Subjects			
< 65 years	35	29	64
≥ 65 years	8	13	21
Age continuous Units: years			
arithmetic mean	58.0	59.0	
standard deviation	± 8.7	± 9.5	-
Gender categorical Units:			
Female	21	20	41
Male	22	22	44
Enrollment by geographical region Units: Subjects			
Europe	29	28	57
North America	12	11	23
Latin America	2	3	5
Race Units: Subjects			
Asian	1	0	1
White	23	21	44
Other	1	0	1
Not Applicable	18	21	39
Ethnicity Units: Subjects			
Hispanic or Latino	6	6	12
Not Hispanic or Latino	19	15	34
Missing	18	21	39
PAH-specific therapy Units: Subjects			
Yes	27	27	54
No	16	15	31
Body Mass Index (BMI) Units: kg/m2			
arithmetic mean	29.01	29.33	
standard deviation	± 4.79	± 4.04	-
Time since portal hypertension diagnosis			

Units: months			
median	23	31	
inter-quartile range (Q1-Q3)	5 to 80	4 to 69	-
Time since PAH diagnosis			
Units: months			
median	7	12	
inter-quartile range (Q1-Q3)	2 to 33	1 to 37	-
Pulmonary vascular resistance (PVR) at baseline (calculated)			
Units: dyn*sec/cm5			
arithmetic mean	552.4	521.7	
standard deviation	± 192.8	± 163.3	-

Subject analysis sets

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) includes all randomized patients who received at least one dose of study treatment in the DB treatment period and have a baseline value for the primary endpoint (pulmonary vascular resistance). Subjects are evaluated according to the treatment to which they were assigned (which may be different from the treatment they have received).

Reporting group values	Full analysis set (FAS)		
Number of subjects	85		
Age categorical			
Units: Subjects			
< 65 years	64		
≥ 65 years	21		
Age continuous			
Units: years			
arithmetic mean	58.5		
standard deviation	± 9.1		
Gender categorical			
Units:			
Female	41		
Male	44		
Enrollment by geographical region			
Units: Subjects			
Europe	57		
North America	23		
Latin America	5		
Race			
Units: Subjects			
Asian	1		
White	44		
Other	1		
Not Applicable	29		
Ethnicity			
Units: Subjects			
Hispanic or Latino	12		
Not Hispanic or Latino	34		

Missing	39		
PAH-specific therapy Units: Subjects			
Yes	54		
No	31		
Body Mass Index (BMI) Units: kg/m2			
arithmetic mean	29.17		
standard deviation	± 4.41		
Time since portal hypertension diagnosis Units: months			
median	25		
inter-quartile range (Q1-Q3)	5 to 76		
Time since PAH diagnosis Units: months			
median	10		
inter-quartile range (Q1-Q3)	2 to 36		
Pulmonary vascular resistance (PVR) at baseline (calculated) Units: dyn*sec/cm5			
arithmetic mean	537.2		
standard deviation	± 178.4		

End points

End points reporting groups

Reporting group title	Macitentan 10 mg
Reporting group description:	
Macitentan 10 mg to be taken once daily, oral use, film-coated tablet	
Reporting group title	Placebo
Reporting group description:	
Macitentan-matching placebo to be taken once daily, oral use, film-coated tablet	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set (FAS) includes all randomized patients who received at least one dose of study treatment in the DB treatment period and have a baseline value for the primary endpoint (pulmonary vascular resistance). Subjects are evaluated according to the treatment to which they were assigned (which may be different from the treatment they have received).	

Primary: Change from baseline to Week 12 in pulmonary vascular resistance (PVR)

End point title	Change from baseline to Week 12 in pulmonary vascular resistance (PVR)
End point description:	
The relative change from baseline to Week 12 in PVR is expressed as a ratio of Week 12 to baseline PVR.	
End point type	Primary
End point timeframe:	
From enrollment/baseline to Week 12 in the DB treatment period	

End point values	Macitentan 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	42		
Units: ratio of baseline PVR				
geometric mean (confidence interval 95%)	0.63 (0.58 to 0.67)	0.98 (0.91 to 1.05)		

Statistical analyses

Statistical analysis title	Analysis of change in PVR
Statistical analysis description:	
The null hypothesis (change of PVR at Week 12 as a ratio of baseline PVR in subjects treated with placebo or macitentan is the same) is tested on the primary endpoint by means of an analysis of covariance (ANCOVA) model on the log(e) transformed ratios of PVR at Week 12 to baseline PVR.	
Comparison groups	Macitentan 10 mg v Placebo

Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	0.72

Notes:

[1] - ANCOVA model adjusted by treatment, background PAH-specific therapy at baseline and region as factors, and log-transformed PVR at baseline as a covariate.

Secondary: Change from baseline to Week 12 in 6-minute walk distance (6MWD)

End point title	Change from baseline to Week 12 in 6-minute walk distance (6MWD)

End point description:

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.

End point type	Secondary

End point timeframe:

From enrollment/baseline to Week 12 in the DB treatment period

End point values	Macitentan 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	42		
Units: meter				
arithmetic mean (standard deviation)				
6MWD at baseline	385.8 (± 99.97)	383.2 (± 108.90)		
6MWD at Week 12	392.2 (± 98.46)	380.8 (± 114.98)		
Change of 6MWD from baseline to Week 12	6.4 (± 65.74)	-2.4 (± 43.65)		

Statistical analyses

Statistical analysis title	Analysis of change in 6MWD at Week 12
Comparison groups	Macitentan 10 mg v Placebo

Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.4264 [3]
Method	mixed-effect model repeated measure
Parameter estimate	Least squares (LS) mean difference
Point estimate	9.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.5
upper limit	33.95

Notes:

[2] - The main analysis on 6MWD was performed using a mixed-effect model repeated measure (MMRM) adjusted for treatment, visit, region, PAH-specific therapy at baseline, and treatment-by-visit interaction as factors, and baseline 6MWD and WHO functional class (FC) as covariates.

[3] - No adjustment was made for multiplicity for secondary endpoints, therefore all corresponding p-values provided are of an exploratory nature.

Secondary: Change from baseline to Week 12 in WHO functional class (FC)

End point title	Change from baseline to Week 12 in WHO functional class (FC)

End point description:

Changes from baseline to Week 12 in WHO FC were dichotomized as worsening (i.e., change > 0) versus no change or improvement (i.e., 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 (e.g. 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 (e.g. dyspnea and/or fatigue) and inability to carry out any physical activity without symptoms. Patients in class IV manifest signs of right heart failure.

End point type	Secondary

End point timeframe:

From enrollment/baseline to Week 12 in the DB treatment period

End point values	Macitentan 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	42		
Units: subjects				
WHO FC I at baseline	1	1		
WHO FC II at baseline	27	23		
WHO FC III at baseline	15	18		
WHO FC IV at baseline	0	0		
WHO FC I at Week 12	3	4		
WHO FC II at Week 12	27	23		
WHO FC III at Week 12	13	15		
WHO FC IV at Week 12	0	0		
Improved from baseline to Week 12	9	7		
Worsened from baseline to Week 12	6	1		
Unchanged from baseline to Week 12	28	34		

Statistical analyses

Statistical analysis title	Analysis of worsening in WHO FC at Week 12

Statistical analysis description:

A logistic regression model (exact) adjusted for treatment, PAH-specific therapy at baseline, and region as covariates was used to analyze worsening in WHO FC.

Comparison groups	Macitentan 10 mg v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1278 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	6.253
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.714
upper limit	298.376

Notes:

[4] - No adjustment was made for multiplicity for secondary endpoints, therefore all corresponding p-values provided are of an exploratory nature.

Secondary: Change from baseline to Week 12 in the biomarker N-terminal pro b-type natriuretic peptide (NT-proBNP)

End point title	Change from baseline to Week 12 in the biomarker N-terminal pro b-type natriuretic peptide (NT-proBNP)

End point description:

NT-proBNP functions as a strong indicator of prognosis in patients with pulmonary hypertension (PH). The relative change from baseline to Week 12 in NT-proBNP is expressed as a ratio of Week 12 to baseline NT-proBNP.

End point type	Secondary

End point timeframe:

From enrollment/baseline to Week 12 in the DB treatment period

End point values	Macitentan 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	40		
Units: ratio of baseline NT-proBNP				
geometric mean (confidence interval 95%)	0.86 (0.67 to 1.11)	1.04 (0.81 to 1.34)		

Statistical analyses

Statistical analysis title	Analysis of change in NT-proBNP
Comparison groups	Macitentan 10 mg v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3951 [5]
Method	ANCOVA
Parameter estimate	ratio of geometric means
Point estimate	0.874
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.639
upper limit	1.196

Notes:

[5] - No adjustment was made for multiplicity for secondary endpoints, therefore all corresponding p-values provided are of an exploratory nature.

Secondary: Change from baseline to Week 12 in mean right atrial pressure (mRAP)

End point title	Change from baseline to Week 12 in mean right atrial pressure (mRAP)

End point description:

End point type	Secondary

End point timeframe:

From enrollment/baseline to Week 12 in the DB treatment period

End point values	Macitentan 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: mmHg				
arithmetic mean (standard deviation)				
mRAP at baseline	7.3 (± 3.74)	6.7 (± 3.60)		
mRAP at Week 12	9.0 (± 5.32)	7.0 (± 2.93)		
Change in mRAP from baseline to Week 12	1.6 (± 5.55)	0.3 (± 3.29)		

Statistical analyses

Statistical analysis title	Analysis of change in mRAP
Comparison groups	Macitentan 10 mg v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0637 [6]
Method	ANCOVA
Parameter estimate	Least squares (LS) mean difference
Point estimate	1.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	3.44

Notes:

[6] - No adjustment was made for multiplicity for secondary endpoints, therefore all corresponding p-values provided are of an exploratory nature.

Secondary: Change from baseline to Week 12 in mean pulmonary artery pressure (mPAP)

End point title	Change from baseline to Week 12 in mean pulmonary artery pressure (mPAP)

End point description:

End point type	Secondary

End point timeframe:

From enrollment/baseline to Week 12 in the DB treatment period

End point values	Macitentan 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	42		
Units: mmHg				
arithmetic mean (standard deviation)				
mPAP at baseline	46.4 (± 7.89)	43.8 (± 8.52)		
mPAP at Week 12	40.0 (± 7.61)	44.2 (± 8.26)		
Change in mPAP at Week 12	-6.4 (± 4.94)	0.4 (± 7.04)		

Statistical analyses

Statistical analysis title	Analysis of change in mPAP
Comparison groups	Macitentan 10 mg v Placebo

Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	ANCOVA
Parameter estimate	Least squares (LS) mean difference
Point estimate	-5.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	-3.57

Notes:

[7] - No adjustment was made for multiplicity for secondary endpoints, therefore all corresponding p-values provided are of an exploratory nature.

Secondary: Change from baseline to Week 12 in cardiac index

End point title	Change from baseline to Week 12 in cardiac index

End point description:

End point type	Secondary

End point timeframe:

From enrollment/baseline to Week 12 in the DB treatment period

End point values	Macitentan 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	42		
Units: L/min/m2				
arithmetic mean (standard deviation)				
Cardiac index at baseline	3.1 (± 0.83)	2.9 (± 0.76)		
Cardiac index at Week 12	3.7 (± 1.04)	3.0 (± 0.82)		
Change in Cardiac index at Week 12	0.6 (± 0.8)	0.1 (± 0.6)		

Statistical analyses

Statistical analysis title	Analysis of change in cardiac index
Comparison groups	Macitentan 10 mg v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009 [8]
Method	ANCOVA
Parameter estimate	Least squares (LS) mean difference
Point estimate	0.52

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.81

Notes:

[8] - No adjustment was made for multiplicity for secondary endpoints, therefore all corresponding p-values provided are of an exploratory nature.

Secondary: Change from baseline to Week 12 in total pulmonary resistance (TPR)

End point title	Change from baseline to Week 12 in total pulmonary resistance (TPR)

End point description:

End point type	Secondary

End point timeframe:

From enrollment/baseline to Week 12 in the DB treatment period

End point values	Macitentan 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	42		
Units: dyn*sec/cm5				
arithmetic mean (standard deviation)				
TPR at baseline	689.3 (± 228.59)	671.5 (± 199.73)		
TRP at Week 12	489.4 (± 157.13)	653.1 (± 197.88)		
Change in TPR from baseline to Week 12	-199.8 (± 163.06)	-18.3 (± 135.28)		

Statistical analyses

Statistical analysis title	Analysis of change in TPR
Comparison groups	Macitentan 10 mg v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	ANCOVA
Parameter estimate	Least squares (LS) mean difference
Point estimate	-171.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-223.67
upper limit	-119.3

Notes:

[9] - No adjustment was made for multiplicity for secondary endpoints, therefore all corresponding p-values provided are of an exploratory nature.

Secondary: Change from baseline to Week 12 in mixed venous oxygen saturation (SVO2)

End point title	Change from baseline to Week 12 in mixed venous oxygen saturation (SVO2)

End point description:

End point type	Secondary

End point timeframe:

From enrollment/baseline to Week 12 in the DB treatment period

End point values	Macitentan 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	41		
Units: percent				
arithmetic mean (standard deviation)				
SVO2 at baseline	69.2 (± 9.87)	69.9 (± 5.34)		
SVO2 at Week 12	70.3 (± 7.07)	70.7 (± 8.58)		
Change in SVO2 from baseline to Week 12	1.1 (± 6.70)	0.8 (± 7.81)		

Statistical analyses

Statistical analysis title	Analysis of change in SVO2
Comparison groups	Macitentan 10 mg v Placebo
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9844 [10]
Method	ANCOVA
Parameter estimate	Least squares (LS) mean difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.85
upper limit	2.91

Notes:

[10] - No adjustment was made for multiplicity for secondary endpoints, therefore all corresponding p-values provided are of an exploratory nature.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From double-blind study treatment initiation up to 30 days after study treatment discontinuation or start of open label period

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Macitentan 10 mg

Reporting group description:

Macitentan 10 mg to be taken once daily, film-coated tablet, oral use

Reporting group title	Placebo

Reporting group description:

Macitentan-matching placebo to be taken once daily, film-coated tablet, oral use

Serious adverse events	Macitentan 10 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 43 (20.93%)	6 / 42 (14.29%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	1 / 43 (2.33%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Aneurysm repair			
subjects affected / exposed	0 / 43 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Localised oedema			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Oedema peripheral			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Alveolitis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary toxicity			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Troponin I increased			

subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Vascular procedure complication			
subjects affected / exposed	0 / 43 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	2 / 43 (4.65%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 43 (2.33%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Localised infection			
subjects affected / exposed	0 / 43 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Macitentan 10 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 43 (51.16%)	22 / 42 (52.38%)	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	3 / 43 (6.98%)	0 / 42 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 43 (16.28%)	7 / 42 (16.67%)	
occurrences (all)	10	8	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	10 / 43 (23.26%)	5 / 42 (11.90%)	
occurrences (all)	13	6	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 43 (2.33%)	4 / 42 (9.52%)	
occurrences (all)	1	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 43 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 43 (0.00%)	5 / 42 (11.90%)	
occurrences (all)	0	6	
Pain in extremity			
subjects affected / exposed	2 / 43 (4.65%)	3 / 42 (7.14%)	
occurrences (all)	2	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 43 (9.30%)	0 / 42 (0.00%)	
occurrences (all)	4	0	
Metabolism and nutrition disorders			
Hypokalaemia			

subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 2	6 / 42 (14.29%) 6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 January 2015	Amendment 1, resulting in Global Protocol Version 2: • Visit window was changed to ± 4 days from ± 7 days to ensure patients had enough study treatment until the next visit. • Reference to hepatic event questionnaire was removed as this form was removed from the electronic Case Report Form (eCRF) • Daclatasvir was added as permitted Hepatitis C medication following its approval • Analysis of urea was removed as it was not needed in addition to blood urea nitrogen. • NT-proBNP storage/shipping text was further clarified • It was clarified that laboratory assessments to be used for eligibility assessment were those performed at Visit 1 / Screening (not Visit 2 / Randomization). • A urine dipstick pregnancy test was added to the assessments at Visit 2 / Randomization in order to have the result prior to treatment assignment. • It was clarified that hepatic vein catheterization (HVC) was not mandatory • It was clarified that PAH or PoPH medications stopped within 3 months prior to randomization were required to be documented in the eCRF.
21 April 2016	Amendment 2, resulting in Global Protocol Version 3: • It was clarified that local laboratory assessments were allowed in order to simplify eligibility assessment and implementation of the stopping rule (i.e., for calculating Model for End-Stage Liver Disease (MELD) score and/or Child-Pugh classification) at Week 12. It was further clarified that the central laboratory kit was required to be used in parallel to the use of local laboratory assessments. • It was clarified that study treatment was allowed to be continued in case of orthotopic liver transplantation (OLT) during the OL period of the study, based on medical consideration. • It was allowed to perform the pharmacokinetic (PK) substudy closer to the patient's home to ease participation • Certain eligibility criteria were modified based on medical considerations, e.g., exclusion criterion 15: transplant expected within 3 months removed; exclusion 21: calcium channel blockers (CCBs) moved to exclusion 20; beta blockers moved to exclusion 10) • The list of allowed and forbidden medications was updated with newly approved antiviral medications • It was clarified that screening started on the day of ICF signature • The definition of the Full Analysis Set was modified to include patients for whom post-baseline PVR was imputed

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported