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	31 October 2018

Results information

Result version number	v2 (current)
This version publication date	11 November 2019
First version publication date	09 November 2018
Version creation reason	

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)	
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	31 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 October 2018
Was the trial ended prematurely?	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 participants were screened and 85 participants were randomized (43 to macitentan 10 mg once daily and 42 to matching placebo) and received double-blind (DB) study treatment. Overall, 80 participants who completed DB treatment period entered the open-label (OL) treatment period and 33 participants in open-label extension (OLE) period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Macitentan 10 mg

Arm description:

Participants received Macitentan 10 milligram (mg) film-coated tablets orally once daily for 12 weeks in Double-blind treatment period.

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:

Participants received Macitentan 10 milligram (mg) film-coated tablets orally once daily.

Arm title	Placebo

Arm description:

Participants received Macitentan matching placebo film-coated tablets orally once daily for 12 weeks in Double-blind treatment period.

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:

Participants received Macitentan matching placebo film-coated tablets orally 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	-

Period 2

Period 2 title	Open-label (OL) treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Macitentan 10 mg

Arm description:

Participants received Macitentan 10 milligram (mg) film-coated tablets orally once daily for 12 weeks in Double-blind treatment period. Participants who completed DB treatment period continued to receive macitentan 10 mg for 12 weeks (up to Week 24) in OL treatment period.

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:

Participants received Macitentan 10 milligram (mg) film-coated tablets orally once daily.

Number of subjects in period 2	Macitentan 10 mg
Started	80
Completed	71
Not completed	9
Consent withdrawn by subject	2
Physician decision	3
Death	4

Period 3

Period 3 title	OL Extension Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Macitentan 10 mg

Arm description:

Participants received Macitentan 10 milligram (mg) film-coated tablets orally once daily for 12 weeks in Double-blind treatment period. Participants who completed DB treatment period continued to receive macitentan 10 mg for 12 weeks (up to Week 24) in OL treatment period . Participants (who were randomized at French sites) who completed the core phase of the study as scheduled and opted to continue receiving OL study treatment continued to receive macitentan 10 mg in OLE period.

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:

Participants received Macitentan 10 milligram (mg) film-coated tablets orally once daily.

Number of subjects in period 3[1]	Macitentan 10 mg
Started	33
Completed	27
Not completed	6
Consent withdrawn by subject	1
Physician decision	3
Death	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Subjects are different as randomized subjects only at French sites who completed the core phase of study and opted to continue receiving OL study treatment continued to receive macitentan 10 mg in OLE period.

Baseline characteristics

Reporting groups	
Reporting group title	Macitentan 10 mg
Reporting group description:	
Participants received Macitentan 10 milligram (mg) film-coated tablets orally once daily for 12 weeks in Double-blind treatment period.	
Reporting group title	Placebo
Reporting group description:	
Participants received Macitentan matching placebo film-coated tablets orally once daily for 12 weeks in Double-blind treatment period.	

Reporting group values	Macitentan 10 mg	Placebo	Total
Number of subjects	43	42	85
Title for AgeCategorical Units: subjects			
Adults (18-64 years)	35	29	64
From 65 to 84 years	8	13	21
Title for AgeContinuous Units: years			
arithmetic mean	58.4	59.0	
standard deviation	± 9.05	± 9.5	-
Title for Gender Units: subjects			
Female	21	20	41
Male	22	22	44
Enrollment by geographical region Units: Subjects			
United States	12	11	23
Brazil	2	3	5
Czech Republic	1	3	4
France	18	21	39
Germany	4	4	8
Spain	4	0	4
United Kingdom	2	0	2
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
Unknown or Not Reported	18	21	39
PAH-specific therapy Units: Subjects			
Yes-PAH	27	27	54

No-PAH	16	15	31

Body Mass Index (BMI) at baseline Units: Kilogram per meter^2 (Kg/m^2) arithmetic mean standard deviation	 9.01 ± 4.79	 29.33 ± 4.04	 -
Time since portal hypertension diagnosis Units: Months median inter-quartile range (Q1-Q3)	 23 5 to 80	 31 4 to 69	 -
Time since PAH diagnosis Units: Months median inter-quartile range (Q1-Q3)	 7 2 to 33	 12 1 to 37	 -
Pulmonary vascular resistance (PVR) at baseline (calculated) Units: Dyn*sec/cm^5 arithmetic mean standard deviation	 552.4 ± 192.8	 521.7 ± 163.3	 -

End points

End points reporting groups

Reporting group title	Macitentan 10 mg
Reporting group description:	
Participants received Macitentan 10 milligram (mg) film-coated tablets orally once daily for 12 weeks in Double-blind treatment period.	
Reporting group title	Placebo
Reporting group description:	
Participants received Macitentan matching placebo film-coated tablets orally once daily for 12 weeks in Double-blind treatment period.	
Reporting group title	Macitentan 10 mg
Reporting group description:	
Participants received Macitentan 10 milligram (mg) film-coated tablets orally once daily for 12 weeks in Double-blind treatment period. Participants who completed DB treatment period continued to receive macitentan 10 mg for 12 weeks (up to Week 24) in OL treatment period.	
Reporting group title	Macitentan 10 mg
Reporting group description:	
Participants received Macitentan 10 milligram (mg) film-coated tablets orally once daily for 12 weeks in Double-blind treatment period. Participants who completed DB treatment period continued to receive macitentan 10 mg for 12 weeks (up to Week 24) in OL treatment period . Participants (who were randomized at French sites) who completed the core phase of the study as scheduled and opted to continue receiving OL study treatment continued to receive macitentan 10 mg in OLE period.	
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. Full Analysis Set(FAS): All randomized participants who received at least one dose of study drug in DB treatment, have baseline value for PVR, evaluated As per assigned treatment. Here, 'N'(number of participants analyzed included population included participants with available baseline data.

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:

Full Analysis Set(FAS): All randomized participants who received at least one dose of study drug in DB treatment, have baseline value for PVR, evaluated As per assigned treatment. Here, 'N'(number of participants analyzed included population included participants with available baseline data.

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	46.4 (± 7.89)	43.8 (± 8.52)		
Cardiac index at Week 12	40.0 (± 7.61)	44.2 (± 8.26)		
Change in Cardiac index at Week 12	-6.4 (± 4.94)	0.4 (± 7.04)		

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:

Full Analysis Set(FAS): All randomized participants who received at least one dose of study drug in DB treatment, have baseline value for PVR, evaluated As per assigned treatment. Here, 'N'(number of participants analyzed included population included participants with available baseline data.

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:	
Up to 3.4 years	
Adverse event reporting additional description:	
The Safety Set (SS) included all participants who received at least one dose of study treatment.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Double-Blind (DB) Period: Macitentan 10 mg
Reporting group description:	
Participants received Macitentan 10 milligram (mg) film-coated tablets orally once daily for 12 weeks during DB treatment period.	
Reporting group title	DB Period: Placebo
Reporting group description:	
Participants received Macitentan matching placebo film-coated tablets orally once daily for 12 weeks during DB treatment period.	
Reporting group title	Open-Label (OL) Period: Macitentan 10 mg
Reporting group description:	
Participants received Macitentan 10 milligram (mg) film-coated tablets orally once daily for 12 weeks in Double-blind treatment period. Participants who completed DB treatment period continued to receive macitentan 10 mg for 12 weeks (up to Week 24) in OL treatment period	
Reporting group title	OL Extension Period: Macitentan 10 mg
Reporting group description:	
Participants received Macitentan 10 milligram (mg) film-coated tablets orally once daily for 12 weeks in Double-blind treatment period. Participants who completed DB treatment period continued to receive macitentan 10 mg for 12 weeks (up to Week 24) in OL treatment period . Participants (who were randomized at French sites) who completed the core phase of the study as scheduled and opted to continue receiving OL study treatment continued to receive macitentan 10 mg in OLE period.	

Serious adverse events	Double-Blind (DB) Period: Macitentan 10 mg	DB Period: Placebo	Open-Label (OL) Period: Macitentan 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 43 (20.93%)	6 / 42 (14.29%)	18 / 80 (22.50%)
number of deaths (all causes)	0	0	4
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular Carcinoma			
subjects affected / exposed	1 / 43 (2.33%)	2 / 42 (4.76%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Malignant Ascites			

subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Adenocarcinoma			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Testis Cancer			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Aneurysm Repair			
subjects affected / exposed	0 / 43 (0.00%)	1 / 42 (2.38%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised Oedema			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema Peripheral			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Priapism			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute Pulmonary Oedema			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alveolitis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Arterial Hypertension			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary Toxicity			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Liver Function Test Increased			

subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin I Increased			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus Fracture			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural Haematoma			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vascular Procedure Complication			
subjects affected / exposed	0 / 43 (0.00%)	1 / 42 (2.38%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left Ventricular Failure			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Right Ventricular Failure			
subjects affected / exposed	2 / 43 (4.65%)	1 / 42 (2.38%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Haemorrhagic Stroke			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic Encephalopathy			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron Deficiency Anaemia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal Vascular Ectasia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Angiodysplasia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal Obstruction			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Melaena			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Portal Hypertensive Gastropathy			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic Failure			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 43 (2.33%)	1 / 42 (2.38%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chronic Kidney Disease			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteitis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			

subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia Pyelonephritis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Infection			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Staphylococcal Infection			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised Infection			
subjects affected / exposed	0 / 43 (0.00%)	1 / 42 (2.38%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes Mellitus			

subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid Overload			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	OL Extension Period: Macitentan 10 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 33 (33.33%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular Carcinoma			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant Ascites			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal Adenocarcinoma			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Testis Cancer			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Aneurysm Repair			

subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Localised Oedema			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oedema Peripheral			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Priapism			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute Pulmonary Oedema			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Alveolitis			

subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary Arterial Hypertension			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary Toxicity			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Liver Function Test Increased			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Troponin I Increased			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Humerus Fracture				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural Haematoma				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular Procedure Complication				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial Fibrillation				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Left Ventricular Failure				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Right Ventricular Failure				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Haemorrhagic Stroke				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hepatic Encephalopathy				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			

Presyncope				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Iron Deficiency Anaemia				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Tinnitus				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal Pain				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ascites				

subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Duodenal Vascular Ectasia				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal Angiodysplasia				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal Haemorrhage				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal Obstruction				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Portal Hypertensive Gastropathy				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatic Failure				

subjects affected / exposed	1 / 33 (3.03%)		
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	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic Kidney Disease			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteitis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia Pyelonephritis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Lung Infection				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal Infection				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Localised Infection				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Diabetes Mellitus				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fluid Overload				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Double-Blind (DB) Period: Macitentan 10 mg	DB Period: Placebo	Open-Label (OL) Period: Macitentan 10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 43 (60.47%)	23 / 42 (54.76%)	45 / 80 (56.25%)
Investigations			
Haemoglobin Decreased			
subjects affected / exposed	3 / 43 (6.98%)	0 / 42 (0.00%)	3 / 80 (3.75%)
occurrences (all)	3	0	3
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 43 (4.65%)	2 / 42 (4.76%)	5 / 80 (6.25%)
occurrences (all)	2	2	7
Headache			
subjects affected / exposed	7 / 43 (16.28%)	7 / 42 (16.67%)	10 / 80 (12.50%)
occurrences (all)	10	8	11
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 43 (4.65%)	0 / 42 (0.00%)	9 / 80 (11.25%)
occurrences (all)	3	0	12
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 42 (2.38%)	4 / 80 (5.00%)
occurrences (all)	0	2	6
Influenza Like Illness			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	3 / 80 (3.75%)
occurrences (all)	0	0	3
Oedema Peripheral			
subjects affected / exposed	10 / 43 (23.26%)	5 / 42 (11.90%)	13 / 80 (16.25%)
occurrences (all)	13	6	16
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 43 (2.33%)	4 / 42 (9.52%)	1 / 80 (1.25%)
occurrences (all)	1	6	1
Respiratory, thoracic and mediastinal			

disorders			
Dyspnoea			
subjects affected / exposed	1 / 43 (2.33%)	2 / 42 (4.76%)	3 / 80 (3.75%)
occurrences (all)	1	2	3
Cough			
subjects affected / exposed	0 / 43 (0.00%)	3 / 42 (7.14%)	1 / 80 (1.25%)
occurrences (all)	0	3	1
Hypoxia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
Oropharyngeal Pain			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Pain in Extremity			
subjects affected / exposed	2 / 43 (4.65%)	3 / 42 (7.14%)	6 / 80 (7.50%)
occurrences (all)	2	3	7
Back Pain			
subjects affected / exposed	2 / 43 (4.65%)	1 / 42 (2.38%)	1 / 80 (1.25%)
occurrences (all)	2	1	2
Muscle Spasms			
subjects affected / exposed	0 / 43 (0.00%)	5 / 42 (11.90%)	3 / 80 (3.75%)
occurrences (all)	0	6	3
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 43 (9.30%)	0 / 42 (0.00%)	3 / 80 (3.75%)
occurrences (all)	4	0	3
Nasopharyngitis			
subjects affected / exposed	2 / 43 (4.65%)	2 / 42 (4.76%)	3 / 80 (3.75%)
occurrences (all)	3	2	3
Rhinitis			

subjects affected / exposed	2 / 43 (4.65%)	0 / 42 (0.00%)	4 / 80 (5.00%)
occurrences (all)	2	0	6
Sinusitis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 43 (4.65%)	6 / 42 (14.29%)	2 / 80 (2.50%)
occurrences (all)	2	6	2

Non-serious adverse events	OL Extension Period: Macitentan 10 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 33 (78.79%)		
Investigations			
Haemoglobin Decreased			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	6		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Influenza Like Illness			

subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Oedema Peripheral			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	6		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		
Cough			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Hypoxia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Oropharyngeal Pain			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
Pain in Extremity			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Back Pain			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Muscle Spasms			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		

Infections and infestations			
Bronchitis			
subjects affected / exposed	13 / 33 (39.39%)		
occurrences (all)	23		
Nasopharyngitis			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Rhinitis			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	12		
Sinusitis			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		

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