Clinical trial results:
Prospective, Multi-center, Double-blind, Randomized, Placebo-controlled, Parallel-group
Study Assessing the Efficacy and Safety of Macitentan in Fontan-palliated Adult and Adolescent Subjects

Summary

EudraCT number	2016-003320-23
Trial protocol	GB DE DK FR PL IE CZ
Global end of trial date	26 July 2021

Results information

Result version number	v1 (current)
This version publication date	09 February 2022
First version publication date	09 February 2022

Trial information

Trial identification

Sponsor protocol code	AC-055H301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03153137
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, CH-4123
Public contact	Clinical Registry Group, Actelion Pharmaceuticals Ltd, clinicaltrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Actelion Pharmaceuticals Ltd, clinicaltrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001032-PIP03-19
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 July 2021
Global end of trial reached?	Yes
Global end of trial date	26 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to assess the effect of macitentan on exercise capacity (measured by peak oxygen uptake/consumption [VO2]) in comparison with placebo in Fontan-palliated subjects.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Safety evaluations were based on assessment of treatment-emergent adverse events (AEs) and serious AEs (SAEs), vital signs, and laboratory parameters.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 October 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	China: 6
Country: Number of subjects enrolled	Czechia: 20
Country: Number of subjects enrolled	Denmark: 23
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	Poland: 26
Country: Number of subjects enrolled	Taiwan: 6
Country: Number of subjects enrolled	United States: 22
Worldwide total number of subjects	137
EEA total number of subjects	78

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)	18
Adults (18-64 years)	119
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 137 subjects were randomized and enrolled in the study of which 130 subjects completed the study.

Period 1

Period 1 title	Overall Study (overall 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	Placebo

Arm description:

Subjects received Macitentan matching placebo tablets orally once daily (o.d) with or without food starting Day 1 (Visit 2) up to Week 52.

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:

Subjects received Macitentan matching placebo tablets with or without food.

Arm title	Macitentan

Arm description:

Subjects received Macitentan 10 milligrams (mg) tablet o.d orally with or without food starting Day 1 up to Week 52.

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:

Subjects received Macitentan 10 mg tablets with or without food.

Number of subjects in period 1	Placebo	Macitentan
Started	69	68
Completed	66	64
Not completed	3	4
Consent withdrawn by subject	2	1
Physician decision	-	1
Adverse event, non-fatal	-	2
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received Macitentan matching placebo tablets orally once daily (o.d) with or without food starting Day 1 (Visit 2) up to Week 52.	
Reporting group title	Macitentan
Reporting group description:	
Subjects received Macitentan 10 milligrams (mg) tablet o.d orally with or without food starting Day 1 up to Week 52.	

Reporting group values	Placebo	Macitentan	Total
Number of subjects	69	68	137
Title for AgeCategorical			
Units: subjects			
Adolescents: 12-<18 yrs	10	8	18
Adults: >= 18 yrs	59	60	119
Title for AgeContinuous			
Units: years			
arithmetic mean	24.5	23.2	
standard deviation	± 7.49	± 5.82	-
Title for Gender			
Units: subjects			
Female	25	23	48
Male	44	45	89

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received Macitentan matching placebo tablets orally once daily (o.d) with or without food starting Day 1 (Visit 2) up to Week 52.	
Reporting group title	Macitentan
Reporting group description:	
Subjects received Macitentan 10 milligrams (mg) tablet o.d orally with or without food starting Day 1 up to Week 52.	

Primary: Change in Peak Oxygen Uptake/Consumption (VO2) from Baseline to Week 16

End point title	Change in Peak Oxygen Uptake/Consumption (VO2) from Baseline to Week 16
End point description:	
Change in peak VO2 from baseline to Week 16 was reported. Full analysis set (FAS) included all subjects randomized to the study treatment. (VO2 is a flow = a ratio of a volume by unit of time)	
End point type	Primary
End point timeframe:	
Baseline to Week 16	

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: Milliliter/kilogram/minute (mL/kg/min)				
arithmetic mean (standard deviation)	-0.67 (± 2.657)	-0.16 (± 2.855)		

Statistical analyses

Statistical analysis title	Statistical Analysis Set A
Statistical analysis description:	
Due to adaptive nature of the design, the main analysis was conducted on FAS using the inverse normal combination method with pre-specified weights to combine first and second stage p-values.	
Comparison groups	Placebo v Macitentan
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.193 [2]
Method	ANCOVA
Parameter estimate	Median unbiased estimate and repeated CI
Point estimate	0.62

Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-0.62
upper limit	1.85

Notes:

[1] - For each stage, the p-value from the ANCOVA model including randomized treatment, geographical region, and baseline peak VO2 was used to construct the final adjusted p-value.
[2] - Final adjusted p-value (from weighted inverse normal combination test)

Secondary: Change in Peak VO2 from Baseline over 52 Weeks

End point title	Change in Peak VO2 from Baseline over 52 Weeks

End point description:

Change in peak VO2 from baseline over 52 weeks was reported. FAS included all subjects randomized to the study treatment. The results reported disregard the adaptive nature of the design.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: mL/kg/min				
least squares mean (standard error)	-0.92 (± 0.296)	-0.31 (± 0.293)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Mean Count per Minute of Daily Physical Activity Measured by Accelerometer (PA-Ac) from Baseline to Week 16

End point title	Change in Mean Count per Minute of Daily Physical Activity Measured by Accelerometer (PA-Ac) from Baseline to Week 16

End point description:

Change in mean count per minute of daily PA-Ac from baseline to Week 16 was reported. The daily physical activity (counts/min) of the subject is assessed via accelerometer during daytime. FAS included all subjects randomized to the study treatment. N (number of subjects analyzed) is defined as the number of subjects evaluable for this outcome measure. The results reported disregard the adaptive nature of the design.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	61		
Units: counts				
least squares mean (standard error)	-13.95 (± 13.882)	-3.39 (± 13.536)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment-emergent Adverse Events (AEs) and Treatment-emergent Serious AEs (SAEs)

End point title	Number of Subjects with Treatment-emergent Adverse Events (AEs) and Treatment-emergent Serious AEs (SAEs)

End point description:

An adverse event is any untoward medical event that occurs in a subject administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. SAE is any AE that results in: death, persistent or significant disability/incapacity, requires inpatient hospitalization or prolongation of existing hospitalization, is life-threatening experience, is a congenital anomaly/birth defect and may jeopardize participant and/or may require medical or surgical intervention to prevent one of the outcomes listed above. The Safety analysis set (SS) included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 56 weeks

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: subjects				
Treatment- emergent AEs	44	48		
Treatment- emergent SAEs	9	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with AEs Leading to Premature Discontinuation of Study Treatment

End point title	Number of Subjects with AEs Leading to Premature Discontinuation of Study Treatment

End point description:

Number of subjects with AEs leading to premature discontinuation of study treatment was reported. SS included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: subjects	1	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Systolic and Diastolic Arterial Blood Pressure [BP] from Baseline up to Week 56

End point title	Change in Systolic and Diastolic Arterial Blood Pressure [BP] from Baseline up to Week 56

End point description:

Change in systolic and diastolic arterial BP from baseline up to week 56 was reported. SS included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 56

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
Systolic BP: Week 8	2.5 (± 14.41)	-0.4 (± 11.67)		
Systolic BP: Week 16	0.5 (± 14.68)	-4.6 (± 13.05)		
Systolic BP: Week 32	-6.3 (± 15.09)	-3.1 (± 10.51)		
Systolic BP: Week 52	0.0 (± 12.12)	-4.8 (± 12.08)		
Systolic BP: EOT+1 Day	0.4 (± 12.28)	-4.6 (± 12.21)		
Systolic BP: between EOT+1 and EOT+35 Days	6.5 (± 3.54)	-0.3 (± 8.14)		
Diastolic BP: Week 8	-0.2 (± 5.86)	-0.1 (± 9.57)		
Diastolic BP: Week 16	-0.6 (± 10.06)	-3.1 (± 8.74)		
Diastolic BP: Week 32	1.3 (± 8.64)	-1.4 (± 8.21)		
Diastolic BP: Week 52	1.3 (± 10.84)	-2.8 (± 11.21)		
Diastolic BP: EOT+1 Day	1.7 (± 10.96)	-2.7 (± 10.74)		
Diastolic BP: between EOT+1 and EOT+35 Days	6.5 (± 9.19)	7.2 (± 6.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Pulse Rate from Baseline up to Week 56

End point title	Change in Pulse Rate from Baseline up to Week 56

End point description:

Change in pulse rate from baseline up to week 56 was reported. SS included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to week 56

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: beats per minute (bpm)				
arithmetic mean (standard deviation)				
Week 8	-3.9 (± 12.80)	-5.9 (± 12.07)		
Week 16	0.1 (± 14.76)	-0.1 (± 11.57)		
Week 32	0.2 (± 12.37)	1.1 (± 9.10)		
Week 52	-0.7 (± 11.56)	-2.9 (± 10.25)		
EOT+1 Day	-0.4 (± 12.96)	-2.7 (± 11.13)		
Between EOT+1 and EOT+35 Days	-13.0 (± 16.97)	-1.5 (± 8.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Oxygen Saturation (SpO2) from Baseline up to Week 56

End point title	Change in Oxygen Saturation (SpO2) from Baseline up to Week 56

End point description:

Change in SpO2 from baseline up to week 56 was reported. SS included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to week 56

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: percentage				
arithmetic mean (standard deviation)				
Week 8	0.0 (± 3.20)	1.2 (± 2.78)		
Week 16	0.5 (± 2.57)	0.8 (± 2.75)		
Week 32	0.8 (± 2.94)	1.4 (± 3.73)		
Week 52	1.4 (± 2.77)	0.9 (± 2.99)		
EOT+1 Day	1.2 (± 2.71)	0.9 (± 2.99)		
Between EOT+1 and EOT+35 Days	3.0 (± 1.41)	2.0 (± 4.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Body Weight from Baseline up to Week 56

End point title	Change in Body Weight from Baseline up to Week 56

End point description:

Change in body weight from baseline up to week 56 was reported. SS included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 56

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: kilograms (kg)				
arithmetic mean (standard deviation)				
Week 8	-0.38 (± 1.996)	0.43 (± 1.568)		
Week 16	0.21 (± 2.028)	0.58 (± 2.230)		
Week 32	0.73 (± 2.952)	0.77 (± 3.411)		
Week 52	1.44 (± 3.746)	1.30 (± 4.358)		
EOT+1 Day	1.21 (± 3.732)	1.27 (± 4.178)		
Between EOT+1 and EOT+35 Days	0.55 (± 0.778)	2.53 (± 3.753)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment-emergent Marked Laboratory Abnormalities

End point title	Number of Subjects with Treatment-emergent Marked Laboratory Abnormalities

End point description:

Number of subjects with treatment-emergent marked laboratory abnormalities was reported. SS includes all subjects who received at least one dose of study treatment. n (number analyzed) is defined as number of subjects evaluable for this specified category.

End point type	Secondary

End point timeframe:

Up to 56 weeks

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: subjects				
Haemoglobin: LLL less than (<) 80 (n=69,67)	0	0		
Haemoglobin: LL< 100 (n=69,67)	0	0		
Haemoglobin: HH (Increase in > 20 g/L) (n=69,67)	0	0		
Haemoglobin: HHH (Increase in > 40 g/L (n=69,67)	0	0		
Hematocrit: LLL (< 0.20) (n=69,67)	0	0		
Hematocrit: LL (< 0.28 (female) < 0.32 (male))	0	0		
Hematocrit: HH (> 0.55 (female) > 0.60 (male))	0	0		
Hematocrit: HHH (> 0.65)	0	0		
Platelets: LLL (< 50) (n=69,67)	0	0		
Platelets: LL (< 75) (n=69,67)	2	1		
Platelets: HH (> 600) (n=69,67)	0	0		
Platelets: HHH (> 999) (n=69,67)	0	0		
Leukocytes: LLL (< 1.9) (n=69,67)	0	0		
Leukocytes: HH (> 20.0) (n=69,67)	0	0		
Leukocytes: HHH (> 100.0) (n=69,67)	0	0		
Lymphocytes: LLL (< 0.2) (n=69,67)	0	0		
Lymphocytes: HH (> 4.0) (n=69,67)	0	1		
Lymphocytes: HHH (> 20) (n=69,67)	0	0		
Neutrophils: LLL (< 1.0) (n=69,67)	0	0		
Neutrophils: LL (< 1.5) (n=69,67)	0	2		
Eosinophils: HH (> 5.0) (n=69,67)	0	0		
Prothrombin Intl. Normalized Ratio: HH (≥ 1.5 ULN)	3	5		
Prothrombin Intl. Normalized Ratio: HH (≥ 2.5 ULN)	1	1		
Bilirubin: HH (≥ 2 ULN) (n=69,67)	1	2		
Bilirubin: HHH (≥ 5 ULN) (n=69,67)	0	0		
Alkaline Phosphatase: HH (> 2.5 ULN) (n=69,67)	1	0		

Alkaline Phosphatase: HHH (> 5 ULN) (n=69,67)	0	0		
Glomerular Filtration Rate: LLL (< 30) (n=68,67)	0	0		
Glomerular Filtration Rate: LL (< 60) (n=68,67)	1	1		
Glucose: LLL (< 2.2) (n=68,67)	0	0		
Glucose: LL (< 3.0) (n=68,67)	0	2		
Glucose: HH (> 8.9) (n=68,67)	0	2		
Glucose: HHH (> 13.9) (n=68,67)	0	0		
Triglycerides: HH (> 3.42) (n=68,67)	3	1		
Triglycerides: HHH (> 11.4 (n=68,67)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Hemoglobin from Baseline up to Week 56

End point title	Change in Hemoglobin from Baseline up to Week 56

End point description:

Change in hemoglobin from baseline up to week 56 was reported. SS included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 56

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: grams per liter (g/L)				
arithmetic mean (standard deviation)				
Week 8	0.0 (± 6.59)	-8.7 (± 9.33)		
Week 16	0.0 (± 7.75)	-8.7 (± 8.51)		
Week 32	1.3 (± 8.29)	-7.3 (± 9.84)		
Week 52	-2.9 (± 10.04)	-7.1 (± 10.02)		
EOT+1 Day	-1.6 (± 10.25)	-7.6 (± 10.45)		
Between EOT+1 and EOT+35 Days	-3.7 (± 5.59)	-7.4 (± 16.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Hematocrit from Baseline up to Week 56

End point title	Change in Hematocrit from Baseline up to Week 56

End point description:

Change in hematocrit from baseline up to week 56 was reported. SS included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 56

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: Liter/Liter (L/L)				
arithmetic mean (standard deviation)				
Week 8	0.002 (± 0.027)	-0.030 (± 0.023)		
Week 16	0.003 (± 0.027)	-0.023 (± 0.026)		
Week 32	0.003 (± 0.031)	-0.009 (± 0.028)		
Week 52	-0.010 (± 0.030)	-0.021 (± 0.028)		
EOT+1 Day	-0.005 (± 0.033)	-0.024 (± 0.028)		
Between EOT+1 and EOT+35 Days	-0.015 (± 0.007)	-0.034 (± 0.055)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Erythrocytes and Reticulocytes from Baseline up to Week 56

End point title	Change in Erythrocytes and Reticulocytes from Baseline up to Week 56

End point description:

Change in erythrocytes and reticulocytes from baseline up to week 56 was reported. SS included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 56

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: 10^12 per liter				
arithmetic mean (standard deviation)				
Erythrocytes: Week 8	0.048 (± 0.2461)	-0.297 (± 0.2866)		

Erythrocytes: Week 16	0.012 (± 0.2521)	-0.264 (± 0.2790)		
Erythrocytes: Week 32	-0.031 (± 0.2442)	-0.090 (± 0.2337)		
Erythrocytes: Week 52	-0.096 (± 0.2515)	-0.184 (± 0.2671)		
Erythrocytes: EOT+1 Day	-0.051 (± 0.2895)	-0.241 (± 0.2980)		
Erythrocytes: between EOT+1 and EOT+35 Days	-0.100 (± 0.0000)	-0.228 (± 0.5364)		
Reticulocytes: Week 8	-0.006 (± 0.017)	-0.006 (± 0.016)		
Reticulocytes: Week 16	-0.003 (± 0.026)	-0.001 (± 0.021)		
Reticulocytes: Week 32	-0.003 (± 0.028)	-0.008 (± 0.027)		
Reticulocytes: Week 52	-0.012 (± 0.033)	-0.011 (± 0.023)		
Reticulocytes: EOT+1 Day	-0.010 (± 0.031)	-0.008 (± 0.023)		
Reticulocytes: between EOT+1 and EOT+35 Days	-0.016 (± 0.007)	0.021 (± 0.030)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Leucocytes, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils and Platelets from Baseline up to Week 56

End point title	Change in Leucocytes, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils and Platelets from Baseline up to Week 56

End point description:

Change in leucocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelets from baseline up to week 56 was reported. SS included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 56

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: 10^9/L				
arithmetic mean (standard deviation)				
Leukocytes: Week 8	-0.242 (± 1.7651)	-1.001 (± 1.2096)		
Leukocytes: Week 16	-0.199 (± 1.5490)	-0.378 (± 1.3908)		
Leukocytes: Week 32	0.417 (± 1.1782)	-0.237 (± 1.7224)		

Leukocytes: Week 52	-0.554 (± 1.4050)	-0.715 (± 1.6433)		
Leukocytes: EOT+1 Day	-0.442 (± 1.3504)	-0.594 (± 1.6208)		
Leukocytes: between EOT+1 and EOT+35 Days	-3.535 (± 0.4596)	-0.653 (± 0.9841)		
Neutrophils: Week 8	-0.133 (± 1.3604)	-0.743 (± 0.9864)		
Neutrophils: Week 16	-0.291 (± 1.3547)	-0.373 (± 1.0896)		
Neutrophils: Week 32	0.494 (± 0.9719)	-0.254 (± 1.2012)		
Neutrophils: Week 52	-0.384 (± 1.1619)	-0.627 (± 1.2475)		
Neutrophils: EOT+1 Day	-0.308 (± 1.1214)	-0.536 (± 1.2369)		
Neutrophils: between EOT+1 and EOT+35 Days	-3.560 (± 0.1414)	-0.353 (± 1.2918)		
Lymphocytes: Week 8	-0.113 (± 0.4770)	-0.165 (± 0.2886)		
Lymphocytes: Week 16	0.073 (± 0.4756)	0.042 (± 0.6164)		
Lymphocytes: Week 32	0.047 (± 0.3341)	0.126 (± 0.2269)		
Lymphocytes: Week 52	-0.082 (± 0.4740)	-0.033 (± 0.3890)		
Lymphocytes: EOT+1 Day	-0.060 (± 0.4553)	-0.054 (± 0.3731)		
Lymphocytes: between EOT+1 and EOT+35 Days	0.025 (± 0.2758)	0.098 (± 0.2641)		
Monocytes: Week 8	-0.017 (± 0.1645)	-0.081 (± 0.1400)		
Monocytes: Week 16	0.002 (± 0.1703)	-0.050 (± 0.1202)		
Monocytes: Week 32	-0.018 (± 0.1209)	-0.071 (± 0.1162)		
Monocytes: Week 52	-0.039 (± 0.1380)	-0.077 (± 0.1257)		
Monocytes: EOT+1 Day	-0.034 (± 0.1321)	-0.065 (± 0.1221)		
Monocytes: between EOT+1 and EOT+35 Days	-0.005 (± 0.2333)	-0.053 (± 0.1706)		
Eosinophils: Week 8	-0.003 (± 0.5146)	0.014 (± 0.0816)		
Eosinophils: Week 16	0.016 (± 0.3056)	0.002 (± 0.0755)		
Eosinophils: Week 32	-0.100 (± 0.5447)	0.029 (± 0.1951)		
Eosinophils: Week 52	-0.046 (± 0.3597)	0.015 (± 0.1935)		
Eosinophils: EOT+1 day	-0.041 (± 0.3334)	0.023 (± 0.1758)		
Eosinophils: between EOT+1 and EOT+35 Days	0.005 (± 0.0919)	-0.093 (± 0.1548)		
Basophils: Week 8	-0.002 (± 0.0255)	-0.002 (± 0.0233)		
Basophils: Week 16	0.004 (± 0.0394)	0.000 (± 0.0363)		
Basophils: Week 32	-0.003 (± 0.0354)	0.016 (± 0.0313)		
Basophils: Week 52	-0.003 (± 0.0389)	0.006 (± 0.0281)		

Basophils: EOT+1 Day	0.001 (± 0.0391)	0.004 (± 0.0290)		
Basophils: between EOT+1 and EOT+35 Days	0.000 (± 0.0000)	0.000 (± 0.0316)		
Platelets: Week 8	-5.9 (± 32.85)	-9.1 (± 35.38)		
Platelets: Week 16	-5.4 (± 30.33)	-3.0 (± 28.77)		
Platelets: Week 32	-7.8 (± 33.46)	8.2 (± 33.76)		
Platelets: Week 52	-11.2 (± 29.94)	-5.7 (± 31.75)		
Platelets: EOT+1 Day	-8.8 (± 28.90)	-7.7 (± 30.35)		
Platelets: between EOT+1 and EOT+35 Days	-28.5 (± 3.54)	3.8 (± 7.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Prothrombin Time from Baseline up to Week 56

End point title	Change in Prothrombin Time from Baseline up to Week 56

End point description:

Change in prothrombin time from baseline up to week 56 was reported. SS included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 56

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: Seconds (sec)				
arithmetic mean (standard deviation)				
Week 8	-0.23 (± 3.265)	-0.53 (± 4.567)		
Week 16	0.04 (± 3.921)	0.36 (± 10.868)		
Week 32	1.45 (± 8.261)	0.03 (± 4.135)		
Week 52	-0.64 (± 3.167)	-1.20 (± 3.567)		
EOT+1 Day	-0.99 (± 4.005)	-1.70 (± 5.953)		
Between EOT+1 and EOT+35 Days	0.75 (± 3.041)	1.12 (± 3.699)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Prothrombin Intl. Normalized Ratio from Baseline up to Week 56

End point title	Change in Prothrombin Intl. Normalized Ratio from Baseline up to Week 56

End point description:

Change in prothrombin intl. normalized ratio from baseline up to week 56 was reported. SS included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 56

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: Ratio				
arithmetic mean (standard deviation)				
Week 8	-0.009 (± 0.3216)	-0.054 (± 0.4652)		
Week 16	0.015 (± 0.3806)	0.049 (± 1.1653)		
Week 32	0.171 (± 0.9204)	0.033 (± 0.4597)		
Week 52	-0.044 (± 0.3265)	-0.120 (± 0.3889)		
EOT+1 day	-0.093 (± 0.4460)	-0.168 (± 0.6244)		
Between EOT+1 and EOT+35 days	0.250 (± 0.4950)	-0.020 (± 0.0800)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) and Alkaline Phosphatase (AP) from Baseline up to Week 56

End point title	Change in Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) and Alkaline Phosphatase (AP) from Baseline up to Week 56

End point description:

Change in alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase from baseline up to week 56 was reported. SS included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 56

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: Units per liter (U/L)				
arithmetic mean (standard deviation)				
ALT: Week 8	-0.8 (± 5.57)	-1.8 (± 9.99)		
ALT: Week 16	-0.2 (± 6.86)	-1.6 (± 7.94)		
ALT: Week 32	-0.4 (± 5.62)	-2.1 (± 12.53)		
ALT: Week 52	-0.2 (± 8.11)	-0.3 (± 14.04)		
ALT: EOT+1 day	-0.1 (± 7.72)	1.1 (± 17.41)		
ALT: Between EOT+1 and EOT+35 Days	-4.1 (± 6.12)	8.3 (± 25.48)		
AST: Week 8	-0.7 (± 4.92)	-4.4 (± 2.37)		
AST: Week 16	-0.5 (± 6.13)	-3.9 (± 20.25)		
AST: Week 32	0.9 (± 4.14)	-4.7 (± 22.46)		
AST: Week 52	-0.6 (± 6.83)	-3.2 (± 24.16)		
AST: EOT+1 day	-0.5 (± 6.53)	-0.7 (± 26.60)		
AST: Between EOT+1 and EOT+35 days	-5.0 (± 4.36)	4.5 (± 15.38)		
AP: Week 8	-7.6 (± 19.82)	-8.5 (± 18.14)		
AP: Week 16	-4.7 (± 19.20)	-7.1 (± 22.54)		
AP: Week 32	-10.1 (± 32.43)	-1.1 (± 26.30)		
AP: Week 52	-12.9 (± 34.81)	-7.0 (± 27.63)		
AP: EOT+1 Day	-11.8 (± 32.47)	-9.3 (± 30.51)		
AP: Between EOT+1 and EOT+35 days	-13.0 (± 14.14)	0.3 (± 10.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Bilirubin and Direct Bilirubin from Baseline up to Week 56

End point title	Change in Bilirubin and Direct Bilirubin from Baseline up to Week 56

End point description:

Change in bilirubin and direct bilirubin from baseline up to week 56 was reported. SS included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 56

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: umol/L				
arithmetic mean (standard deviation)				
Bilirubin: Week 8	0.62 (± 5.985)	-1.08 (± 5.693)		
Bilirubin: Week 16	1.98 (± 5.799)	-1.76 (± 7.075)		
Bilirubin: Week 32	1.47 (± 5.285)	0.29 (± 5.052)		
Bilirubin: Week 52	0.69 (± 5.778)	-1.02 (± 5.778)		
Bilirubin: EOT+1 Day	1.13 (± 6.059)	-1.47 (± 7.657)		
Bilirubin: Between EOT+1 and EOT+35 Days	-1.00 (± 1.414)	-0.83 (± 5.115)		
Direct Bilirubin: Week 8	-0.06 (± 1.105)	-0.22 (± 1.149)		
Direct Bilirubin: Week 16	0.24 (± 1.088)	-0.28 (± 1.227)		
Direct Bilirubin: Week 32	0.00 (± 1.029)	-0.04 (± 1.147)		
Direct Bilirubin: Week 52	0.28 (± 1.280)	-0.24 (± 1.228)		
Direct Bilirubin: EOT+1 Day	0.31 (± 1.435)	-0.24 (± 1.138)		
Direct Bilirubin: between EOT+1 and EOT+35 days)	0.50 (± 0.707)	0.17 (± 1.329)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Gamma Glutamyl Transferase from Baseline up to Week 56

End point title	Change in Gamma Glutamyl Transferase from Baseline up to Week 56

End point description:

Change in gamma glutamyl transferase from baseline up to week 56 was reported. SS included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 56

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: Units per liter (U/L)				
arithmetic mean (standard deviation)				
Week 8	-4.8 (± 13.22)	-5.5 (± 12.56)		
Week 16	-4.4 (± 13.79)	0.7 (± 27.43)		

Week 32	-1.3 (± 13.39)	-5.3 (± 23.29)		
Week 52	-3.2 (± 22.40)	-6.7 (± 21.31)		
EOT+1 Day	-1.0 (± 15.98)	-6.4 (± 19.98)		
Between EOT+1 and EOT+35 Days	-58.0 (± 82.02)	-7.2 (± 30.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Creatinine from Baseline up to Week 56

End point title	Change in Creatinine from Baseline up to Week 56

End point description:

Change in creatinine from baseline up to week 56 was reported. SS included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 56

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: umol/L				
arithmetic mean (standard deviation)				
Week 8	-2.0 (± 7.49)	-6.2 (± 7.49)		
Week 16	-1.1 (± 10.72)	-0.3 (± 12.46)		
Week 32	2.2 (± 10.81)	-1.8 (± 13.46)		
Week 52	-1.5 (± 9.52)	0.4 (± 10.00)		
EOT+1 Day	-1.5 (± 9.01)	0.4 (± 10.28)		
Between EOT+1 and EOT+35 Days	3.5 (± 2.12)	-0.8 (± 7.73)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Urea Nitrogen from Baseline up to Week 56

End point title	Change in Urea Nitrogen from Baseline up to Week 56

End point description:

Change in urea nitrogen from baseline up to week 56 was reported. SS included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 56

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
Week 8	-0.30 (± 0.989)	-0.09 (± 1.217)		
Week 16	-0.04 (± 1.043)	0.06 (± 1.278)		
Week 32	0.02 (± 0.955)	-0.25 (± 1.274)		
Week 52	-0.06 (± 1.251)	0.04 (± 1.101)		
EOT+1 Day	-0.02 (± 1.186)	0.02 (± 1.141)		
Between EOT+1 and EOT+35 days)	-1.70 (± 1.414)	-0.17 (± 0.582)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Urate from Baseline up to Week 56

End point title	Change in Urate from Baseline up to Week 56

End point description:

Change in urate from baseline up to week 56 was reported. SS included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 56

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: umol/L				
arithmetic mean (standard deviation)				
Week 8	-0.8 (± 40.76)	-53.6 (± 40.17)		
Week 16	2.8 (± 40.13)	-37.8 (± 40.01)		
Week 32	16.0 (± 39.35)	-56.7 (± 53.18)		
Week 52	1.1 (± 49.36)	-25.8 (± 54.39)		
EOT+1 Day	0.4 (± 46.38)	-27.8 (± 54.24)		

Between EOT+1 and EOT+35 Days	-38.0 (± 4.24)	-10.2 (± 27.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Glucose, Cholesterol, Triglycerides, Sodium, Potassium, Chloride and Calcium from Baseline up to Week 56

End point title	Change in Glucose, Cholesterol, Triglycerides, Sodium, Potassium, Chloride and Calcium from Baseline up to Week 56

End point description:

Change in glucose, cholesterol, triglycerides, sodium, potassium, chloride and calcium from baseline up to week 56 was reported. SS included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to week 56

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
Glucose: Week 8	0.00 (± 1.028)	-0.46 (± 0.914)		
Glucose: Week 16	0.17 (± 1.153)	-0.04 (± 1.022)		
Glucose: Week 32	0.24 (± 0.911)	-0.12 (± 0.850)		
Glucose: Week 52	-0.03 (± 0.883)	-0.28 (± 1.193)		
Glucose: EOT+1 Day	0.03 (± 0.919)	-0.25 (± 1.156)		
Glucose: Between EOT+1 and EOT+35 Days	-0.25 (± 1.202)	-0.28 (± 0.796)		
Cholesterol: Week 8	-0.182 (± 0.3808)	-0.238 (± 0.3807)		
Cholesterol: Week 16	-0.065 (± 0.3994)	-0.190 (± 0.5139)		
Cholesterol: Week 32	0.060 (± 0.5185)	-0.059 (± 0.5364)		
Cholesterol: Week 52	-0.065 (± 0.4308)	-0.093 (± 0.4243)		
Cholesterol: EOT+1 Day	-0.080 (± 0.4273)	-0.126 (± 0.4450)		
Cholesterol: Between EOT+1 and EOT+35 Days	-0.355 (± 0.2616)	-0.042 (± 0.4820)		
Triglycerides: Week 8	-0.061 (± 0.5950)	-0.071 (± 0.3755)		

Triglycerides: Week 16	-0.099 (± 0.3946)	-0.004 (± 0.4244)		
Triglycerides: Week 32	0.123 (± 0.4749)	0.024 (± 0.5126)		
Triglycerides: Week 52	-0.067 (± 0.5191)	-0.020 (± 0.4703)		
Triglycerides: EOT+1 Day	-0.092 (± 0.5069)	-0.010 (± 0.4449)		
Triglycerides: Between EOT+1 and EOT+35 Days	0.160 (± 0.0990)	0.002 (± 0.1848)		
Sodium: Week 8	-0.5 (± 2.02)	-0.2 (± 2.52)		
Sodium: Week 16	-1.1 (± 2.74)	-0.6 (± 2.94)		
Sodium: Week 32	-0.7 (± 3.23)	-0.3 (± 2.44)		
Sodium: Week 52	-1.1 (± 2.28)	-1.0 (± 2.35)		
Sodium: EOT+1 Day	-1.0 (± 2.25)	-0.8 (± 2.36)		
Sodium: Between EOT+1 and EOT+35 Days	2.0 (± 2.83)	0.2 (± 3.71)		
Potassium: Week 8	-0.074 (± 0.3476)	-0.030 (± 0.2876)		
Potassium: Week 16	-0.013 (± 0.3684)	0.030 (± 0.3783)		
Potassium: Week 32	-0.011 (± 0.3957)	-0.033 (± 0.2599)		
Potassium: Week 52	-0.031 (± 0.3354)	-0.003 (± 0.3356)		
Potassium: EOT+1 Day	-0.050 (± 0.3787)	-0.014 (± 0.3464)		
Potassium: Between EOT+1 and EOT+35 Days	0.200 (± 0.1414)	-0.145 (± 0.3062)		
Chloride: Week 8	0.2 (± 1.71)	1.3 (± 2.33)		
Chloride: Week 16	-0.4 (± 2.88)	0.3 (± 2.75)		
Chloride: Week 32	-0.1 (± 2.37)	0.3 (± 2.28)		
Chloride: Week 52	0.4 (± 2.44)	0.4 (± 2.89)		
Chloride: EOT+1 Day	0.3 (± 2.47)	0.5 (± 2.78)		
Chloride: Between EOT+1 and EOT+35 Days	2.5 (± 2.12)	0.3 (± 3.56)		
Calcium: Week 8	-0.006 (± 0.1096)	-0.062 (± 0.0999)		
Calcium: Week 16	-0.002 (± 0.0929)	-0.050 (± 0.0943)		
Calcium: Week 32	0.035 (± 0.0987)	-0.004 (± 0.1271)		
Calcium: Week 52	-0.021 (± 0.1083)	-0.035 (± 0.1093)		
Calcium: EOT+1 Day	-0.017 (± 0.1046)	-0.037 (± 0.1065)		
Calcium: Between EOT+1 and EOT+35 Days	-0.100 (± 0.0990)	0.003 (± 0.1104)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Albumin and Protein from Baseline up to Week 56

End point title	Change in Albumin and Protein from Baseline up to Week 56

End point description:

Change in albumin and protein from baseline up to week 56 was reported. SS included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 56

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: grams per liter (g/L)				
arithmetic mean (standard deviation)				
Albumin: Week 8	-0.74 (± 2.789)	-1.73 (± 2.922)		
Albumin: Week 16	0.61 (± 2.821)	-0.82 (± 3.274)		
Albumin: Week 32	0.79 (± 3.276)	0.38 (± 3.462)		
Albumin: Week 52	-0.08 (± 3.426)	-0.53 (± 3.339)		
Albumin: EOT+1 Day	-0.07 (± 3.248)	-0.80 (± 3.548)		
Albumin: Between EOT+1 and EOT+35 Days	-2.50 (± 3.536)	-2.98 (± 7.443)		
Protein: Week 8	-1.5 (± 4.28)	-3.8 (± 4.38)		
Protein: Week 16	-0.3 (± 4.62)	-1.9 (± 4.51)		
Protein: Week 32	-0.2 (± 4.38)	-0.3 (± 4.60)		
Protein: Week 52	-1.8 (± 5.42)	-2.5 (± 5.56)		
Protein: EOT+1 Day	-1.6 (± 5.10)	-2.7 (± 5.57)		
Protein: Between EOT+1 and EOT+35 Days	-3.5 (± 9.19)	-2.3 (± 3.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Alpha Fetoprotein from Baseline up to Week 56

End point title	Change in Alpha Fetoprotein from Baseline up to Week 56

End point description:

Change in alpha fetoprotein from baseline up to week 56 was reported. SS included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 56

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: micrograms per milliliter (ug/L)				
arithmetic mean (standard deviation)				
Week 8	0.006 (± 0.5537)	-0.061 (± 0.6314)		
Week 16	0.055 (± 0.4373)	0.160 (± 0.5667)		
Week 32	0.033 (± 0.3911)	0.191 (± 0.5959)		
Week 52	0.068 (± 0.5003)	0.240 (± 0.6349)		
EOT+1 Day	0.120 (± 0.6147)	0.236 (± 0.6976)		
Between EOT+1 and EOT+35 Days	-0.050 (± 0.2121)	0.360 (± 0.4879)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cystatin C from Baseline up to Week 56

End point title	Change in Cystatin C from Baseline up to Week 56

End point description:

Change in cystatin C from baseline up to week 56 was reported. SS included all subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 56

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: milligrams per liter (mg/L)				
arithmetic mean (standard deviation)				
Week 8	-0.026 (± 0.0563)	-0.019 (± 0.0782)		
Week 16	-0.017 (± 0.1464)	-0.019 (± 0.0964)		
Week 32	-0.038 (± 0.0659)	-0.021 (± 0.0701)		
Week 52	-0.001 (± 0.0723)	0.010 (± 0.0927)		
EOT+1 Day	-0.009 (± 0.0730)	0.006 (± 0.0865)		
Between EOT+1 and EOT+35 Days	0.035 (± 0.0495)	0.014 (± 0.0991)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 56 weeks	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	Macitentan
Reporting group description:	
Subjects received Macitentan 10 milligrams (mg) tablet o.d orally with or without food starting Day 1 up to Week 52.	
Reporting group title	Placebo
Reporting group description:	
Subjects received Macitentan matching placebo tablets orally once daily (o.d) with or without food starting Day 1 (Visit 2) up to Week 52.	

Serious adverse events	Macitentan	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 68 (19.12%)	9 / 69 (13.04%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neuroendocrine Tumour			
subjects affected / exposed	0 / 68 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Medical Device Removal			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 68 (1.47%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
Haemorrhagic Ovarian Cyst			
subjects affected / exposed	0 / 68 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental Status Changes			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polydipsia Psychogenic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart Rate Increased			

subjects affected / exposed	0 / 68 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International Normalised Ratio Increased			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (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			
Back Injury			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle Fracture			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head Injury			
subjects affected / exposed	0 / 68 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road Traffic Accident			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia Supraventricular			
subjects affected / exposed	0 / 68 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Flutter			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial Tachycardia			
subjects affected / exposed	0 / 68 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 68 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular Tachycardia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypoaesthesia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 68 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congestive Hepatopathy			

subjects affected / exposed	0 / 68 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 68 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess Limb			
subjects affected / exposed	0 / 68 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 68 (1.47%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr Virus Infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Tonsillitis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 69 (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	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 68 (22.06%)	18 / 69 (26.09%)	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 68 (10.29%)	6 / 69 (8.70%)	
occurrences (all)	14	10	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 68 (5.88%)	3 / 69 (4.35%)	
occurrences (all)	4	3	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	2 / 68 (2.94%)	4 / 69 (5.80%)	
occurrences (all)	2	4	
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 68 (1.47%)	4 / 69 (5.80%)	
occurrences (all)	1	6	
Nasopharyngitis			
subjects affected / exposed	4 / 68 (5.88%)	3 / 69 (4.35%)	
occurrences (all)	4	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 August 2018	The overall reason for the amendment was to address concerns from BfArM, regarding the new protocol template by reverting to initial safety monitoring modalities. Clarification of participants' medical care after study completion by confirming that the proposed open-label extension will be accessible to all participants who complete the study, including those who were in the PTOP.
19 November 2018	The overall reason for the amendment was implementation of Advisory Board recommendations to make the protocol more patient-centric by converting 2 site visits to phone calls; reducing the number of monthly safety labs; introducing a flying nurse service to reduce the time commitment for the study; updating contraception requirements for new markets.
18 December 2019	The overall reason for the amendment was replacing the blinded SSRE with an IA/unblinded SSRE; formal testing of secondary endpoints; introducing additional exploratory cardiopulmonary exercise testing (CPET) endpoints; adding clarifications for contraceptive use and study completion; introducing use of estimands for the primary endpoint analyses.
15 July 2020	The overall reason for the amendment was updates to forbidden medication and concomitant therapy sections based on newly identified drug-drug interactions.
19 November 2020	The overall reason for the amendment was to make global safety updates. Align the protocol with Janssen processes as part of the Actelion and Janssen integration. Simplify study-treatment supply and storage information. Add an appendix to facilitate evaluation of exclusion criterion 6.3.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported