Clinical trial results:
A Multi-center, Double-blind, Placebo-controlled Phase 2b Study to Evaluate the Efficacy and Safety of Macitentan in Subjects with Heart Failure with Preserved Ejection Fraction and Pulmonary Vascular Disease

Summary

EudraCT number	2016-003653-15
Trial protocol	DE HU GB DK CZ AT SE ES BG
Global end of trial date	12 March 2021

Results information

Result version number	v1 (current)
This version publication date	24 March 2022
First version publication date	24 March 2022

Trial information

Trial identification

Sponsor protocol code	AC-055G202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03153111
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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 March 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate whether macitentan 10 milligrams (mg) reduced N-terminal pro-brain natriuretic peptide (NT-proBNP) versus placebo at Week 24 in subjects with heart failure with preserved ejection fraction (HFpEF) and pulmonary vascular disease (PVD).

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 Practice (GCP) and applicable regulatory requirements. Safety assessments included analysis of treatment-emergent adverse events (TEAEs), laboratory analyte values, vital sign measurements, electrocardiogram (ECG) data, all-cause hospital admissions up to 30 days after treatment, estimated Glomerular Filtration Rate (GFR), and heart failure (HF) signs/symptoms of special interest reported during the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 August 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	Argentina: 1
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Bulgaria: 10
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Israel: 27
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Russian Federation: 20
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United States: 24

Worldwide total number of subjects	142
EEA total number of subjects	63

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)	18
From 65 to 84 years	112
85 years and over	12

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Out of 143 randomised subjects, 1 subject was randomised by mistake and did not receive any dose of study drug. 142 subjects received the study drug and were analysed.

Period 1

Period 1 title	Overall (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 placebo tablet orally once a day starting from Day 1 up to Week 52.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablet was administered orally once a day starting at Day 1 up to Week 52.

Arm title	Macitentan

Arm description:

Subjects received macitentan 10 milligrams (mg) tablet orally once a day starting from Day 1 up to Week 52.

Arm type	Experimental
Investigational medicinal product name	Macitentan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Macitentan 10 mg tablet was administered orally once a day starting at Day 1 up to Week 52.

Number of subjects in period 1	Placebo	Macitentan
Started	71	71
Completed	62	60
Not completed	9	11
Adverse event, serious fatal	5	2
Consent withdrawn by subject	3	1
Physician decision	-	1
Adverse event, non-fatal	-	2
Adverse event, serious non-fatal	1	4
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo tablet orally once a day starting from Day 1 up to Week 52.	
Reporting group title	Macitentan
Reporting group description:	
Subjects received macitentan 10 milligrams (mg) tablet orally once a day starting from Day 1 up to Week 52.	

Reporting group values	Placebo	Macitentan	Total
Number of subjects	71	71	142
Title for AgeCategorical			
Units: subjects			
Adults (18-64 years)	8	10	18
From 65 to 84 years	57	55	112
85 years and over	6	6	12
Title for AgeContinuous			
Units: years			
arithmetic mean	74.2	72.9	
standard deviation	± 8.25	± 10.11	-
Title for Gender			
Units: subjects			
Female	41	46	87
Male	30	25	55

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo tablet orally once a day starting from Day 1 up to Week 52.	
Reporting group title	Macitentan
Reporting group description:	
Subjects received macitentan 10 milligrams (mg) tablet orally once a day starting from Day 1 up to Week 52.	

Primary: Percent of Baseline N-terminal Pro-brain Natriuretic Peptide (NT-proBNP) Assessed at Week 24

End point title	Percent of Baseline N-terminal Pro-brain Natriuretic Peptide (NT-proBNP) Assessed at Week 24
End point description:	
Percent of baseline NT-proBNP assessed at week 24 was reported. Percent of baseline is calculated as the ratio of the Week 24 NT-proBNP value over baseline value, expressed in percentage. NT-proBNP is one of the best established cardiovascular response markers among all available surrogates in heart failure (HF). Full analysis set (FAS) included subjects which were randomized to double-blind study treatment.	
End point type	Primary
End point timeframe:	
Baseline and Week 24	

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	71		
Units: percentage of baseline NT-proBNP				
geometric mean (geometric coefficient of variation)	106.27 (± 0.55)	108.39 (± 0.65)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Double-blind period
Comparison groups	Placebo v Macitentan
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7923
Method	ANCOVA
Parameter estimate	Geometric mean ratio
Point estimate	1.02

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.88
upper limit	1.19

Secondary: Change from Baseline to Week 24 in the Clinical Summary Score Assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ) Score

End point title	Change from Baseline to Week 24 in the Clinical Summary Score Assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ) Score

End point description:

The KCCQ is a validated health related quality of life measure for heart failure. The KCCQ is a 23-item, self-administered instrument that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life. Clinical summary score is one of the quality of life variable of interest derived from KCCQ. Clinical summary score is the mean of domains: physical limitations score (6 items) and total symptom score (2 items [symptoms frequency and symptom burden]). The score is calculated by summing domain responses and then transforming scores to a 0-100 unit scale with higher scores indicating better health status. FAS included subjects which were randomized to double-blind study treatment. Here, 'N' (number of subjects analyzed) specifies all subjects who were evaluated for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	69		
Units: score on a scale				
arithmetic mean (standard deviation)	0.89 (± 17.72)	-2.37 (± 16.12)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Double-blind period
Comparison groups	Placebo v Macitentan
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2172
Method	ANCOVA
Parameter estimate	Least square mean
Point estimate	-3.5

Confidence interval	
level	90 %
sides	2-sided
lower limit	-8.17
upper limit	1.17
Variability estimate	Standard error of the mean
Dispersion value	2.82

Secondary: Change from Baseline to Week 24 in Accelerometer-assessed Proportion of Time Spent in Light to Vigourous Physical Activity

End point title	Change from Baseline to Week 24 in Accelerometer-assessed Proportion of Time Spent in Light to Vigourous Physical Activity

End point description:

Physical activity is assessed by accelerometer as the proportion of time spent in light to vigorous physical activity based on a threshold of greater than (>)100 activity counts per minute and expressed as change from baseline to Week 24. FAS included subjects which were randomized to double-blind study treatment. Here, 'N' (number of participants analyzed) specifies all subjects who were evaluated for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	30		
Units: proportion of time spent				
arithmetic mean (standard deviation)	-0.005 (± 0.098)	-0.024 (± 0.084)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Double-blind period
Comparison groups	Placebo v Macitentan
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3665
Method	ANCOVA
Parameter estimate	Least square mean
Point estimate	-0.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.05
upper limit	0.02

Variability estimate	Standard error of the mean
Dispersion value	0.02

Secondary: Number of Subjects with Worsening of Heart Failure (WHF) Events Over 52 Weeks

End point title	Number of Subjects with Worsening of Heart Failure (WHF) Events Over 52 Weeks

End point description:

Number of subjects with WHF events were reported. A WHF event includes HF death, hospitalization for WHF or an urgent visit for WHF. FAS included subjects which were randomized to double-blind study treatment.

End point type	Secondary

End point timeframe:

Weeks 16, 24, 36, 52

End point values	Placebo	Macitentan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	71		
Units: subjects				
Week 16	5	12		
Week 24	6	14		
Week 36	9	17		
Week 52	13	18		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 17 months	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Macitentan
Reporting group description:	
Subjects received macitentan 10 milligrams (mg) tablet orally once a day starting at Day 1 up to Week 52.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo tablet orally once a day starting at Day 1 up to Week 52.	

Serious adverse events	Macitentan	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 71 (40.85%)	23 / 71 (32.39%)	
number of deaths (all causes)	2	5	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon Cancer			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatic Carcinoma			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superficial Spreading Melanoma Stage Iv			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Hypotension			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Arterial Occlusive Disease			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Ischaemia			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Organ Dysfunction Syndrome			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 71 (1.41%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema Peripheral			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine Polyp			

subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute Pulmonary Oedema			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumopathy			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (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	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Congestion			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental Status Changes			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Ammonia Increased			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Lactic Acid Increased			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin Decreased			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Enzyme Increased			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (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			
Ankle Fracture			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road Traffic Accident			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Left Ventricular Failure			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Pectoris			

subjects affected / exposed	1 / 71 (1.41%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Unstable			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular Block Complete			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Acute			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	5 / 71 (7.04%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	2 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Right Ventricular Failure			

subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left Ventricular Failure			
subjects affected / exposed	3 / 71 (4.23%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right Ventricular Failure			
subjects affected / exposed	6 / 71 (8.45%)	6 / 71 (8.45%)	
occurrences causally related to treatment / all	1 / 6	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 2	
Sinus Node Dysfunction			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral Ischaemia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Encephalopathy			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			
subjects affected / exposed	0 / 71 (0.00%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 71 (1.41%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Loss Anaemia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diabetic Retinopathy			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (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 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Congestive Hepatopathy			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash Pruritic			

subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 71 (0.00%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Impairment			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 71 (1.41%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle Twitching			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gangrene			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastroenteritis			
subjects affected / exposed	2 / 71 (2.82%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 71 (2.82%)	3 / 71 (4.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyelonephritis Acute			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Shock			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary Tract Infection			
subjects affected / exposed	0 / 71 (0.00%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid Overload			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid Retention			
subjects affected / exposed	2 / 71 (2.82%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (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: 2 %

Non-serious adverse events	Macitentan	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 71 (80.28%)	54 / 71 (76.06%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin Cancer			
subjects affected / exposed	0 / 71 (0.00%)	2 / 71 (2.82%)	
occurrences (all)	0	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 71 (2.82%)	2 / 71 (2.82%)	
occurrences (all)	2	3	
Hypotension			
subjects affected / exposed	3 / 71 (4.23%)	3 / 71 (4.23%)	
occurrences (all)	3	3	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 71 (4.23%)	1 / 71 (1.41%)	
occurrences (all)	3	1	
Fatigue			
subjects affected / exposed	5 / 71 (7.04%)	6 / 71 (8.45%)	
occurrences (all)	5	6	
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 71 (1.41%)	2 / 71 (2.82%)	
occurrences (all)	1	2	
Oedema Peripheral			

subjects affected / exposed	9 / 71 (12.68%)	4 / 71 (5.63%)	
occurrences (all)	13	5	
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	0 / 71 (0.00%)	2 / 71 (2.82%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 71 (2.82%)	4 / 71 (5.63%)	
occurrences (all)	2	6	
Dyspnoea			
subjects affected / exposed	8 / 71 (11.27%)	7 / 71 (9.86%)	
occurrences (all)	9	10	
Nasal Congestion			
subjects affected / exposed	2 / 71 (2.82%)	1 / 71 (1.41%)	
occurrences (all)	2	1	
Pleural Effusion			
subjects affected / exposed	2 / 71 (2.82%)	1 / 71 (1.41%)	
occurrences (all)	2	1	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	2 / 71 (2.82%)	1 / 71 (1.41%)	
occurrences (all)	2	1	
Blood Creatinine Increased			
subjects affected / exposed	3 / 71 (4.23%)	2 / 71 (2.82%)	
occurrences (all)	3	2	
Blood Potassium Increased			
subjects affected / exposed	1 / 71 (1.41%)	2 / 71 (2.82%)	
occurrences (all)	1	2	
Blood Urea Increased			
subjects affected / exposed	4 / 71 (5.63%)	1 / 71 (1.41%)	
occurrences (all)	4	1	
Blood Uric Acid Increased			
subjects affected / exposed	1 / 71 (1.41%)	3 / 71 (4.23%)	
occurrences (all)	1	3	
Glomerular Filtration Rate Decreased			

subjects affected / exposed	2 / 71 (2.82%)	2 / 71 (2.82%)	
occurrences (all)	2	2	
Brain Natriuretic Peptide Increased			
subjects affected / exposed	0 / 71 (0.00%)	2 / 71 (2.82%)	
occurrences (all)	0	2	
Haemoglobin Decreased			
subjects affected / exposed	3 / 71 (4.23%)	3 / 71 (4.23%)	
occurrences (all)	4	4	
Weight Increased			
subjects affected / exposed	2 / 71 (2.82%)	3 / 71 (4.23%)	
occurrences (all)	2	3	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 71 (1.41%)	4 / 71 (5.63%)	
occurrences (all)	1	4	
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	4 / 71 (5.63%)	5 / 71 (7.04%)	
occurrences (all)	4	5	
Angina Pectoris			
subjects affected / exposed	2 / 71 (2.82%)	0 / 71 (0.00%)	
occurrences (all)	2	0	
Atrial Flutter			
subjects affected / exposed	2 / 71 (2.82%)	1 / 71 (1.41%)	
occurrences (all)	2	1	
Cardiac Failure Congestive			
subjects affected / exposed	3 / 71 (4.23%)	1 / 71 (1.41%)	
occurrences (all)	3	1	
Left Ventricular Failure			
subjects affected / exposed	5 / 71 (7.04%)	0 / 71 (0.00%)	
occurrences (all)	6	0	
Palpitations			
subjects affected / exposed	0 / 71 (0.00%)	2 / 71 (2.82%)	
occurrences (all)	0	2	
Right Ventricular Failure			

subjects affected / exposed	5 / 71 (7.04%)	2 / 71 (2.82%)	
occurrences (all)	6	2	
Nervous system disorders			
Cerebral Ischaemia			
subjects affected / exposed	2 / 71 (2.82%)	0 / 71 (0.00%)	
occurrences (all)	2	0	
Dizziness			
subjects affected / exposed	3 / 71 (4.23%)	3 / 71 (4.23%)	
occurrences (all)	3	3	
Headache			
subjects affected / exposed	4 / 71 (5.63%)	1 / 71 (1.41%)	
occurrences (all)	4	1	
Lethargy			
subjects affected / exposed	2 / 71 (2.82%)	1 / 71 (1.41%)	
occurrences (all)	2	1	
Syncope			
subjects affected / exposed	1 / 71 (1.41%)	2 / 71 (2.82%)	
occurrences (all)	1	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 71 (7.04%)	3 / 71 (4.23%)	
occurrences (all)	6	3	
Blood Loss Anaemia			
subjects affected / exposed	2 / 71 (2.82%)	1 / 71 (1.41%)	
occurrences (all)	2	1	
Hypochromic Anaemia			
subjects affected / exposed	2 / 71 (2.82%)	0 / 71 (0.00%)	
occurrences (all)	2	0	
Iron Deficiency Anaemia			
subjects affected / exposed	4 / 71 (5.63%)	1 / 71 (1.41%)	
occurrences (all)	4	1	
Normocytic Anaemia			
subjects affected / exposed	2 / 71 (2.82%)	1 / 71 (1.41%)	
occurrences (all)	2	1	
Gastrointestinal disorders			

Abdominal Pain Upper			
subjects affected / exposed	2 / 71 (2.82%)	0 / 71 (0.00%)	
occurrences (all)	2	0	
Ascites			
subjects affected / exposed	2 / 71 (2.82%)	1 / 71 (1.41%)	
occurrences (all)	2	1	
Diarrhoea			
subjects affected / exposed	2 / 71 (2.82%)	2 / 71 (2.82%)	
occurrences (all)	3	3	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 71 (2.82%)	0 / 71 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 71 (4.23%)	0 / 71 (0.00%)	
occurrences (all)	3	0	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	5 / 71 (7.04%)	2 / 71 (2.82%)	
occurrences (all)	5	3	
Renal Failure			
subjects affected / exposed	2 / 71 (2.82%)	4 / 71 (5.63%)	
occurrences (all)	2	4	
Renal Impairment			
subjects affected / exposed	5 / 71 (7.04%)	1 / 71 (1.41%)	
occurrences (all)	5	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 71 (1.41%)	2 / 71 (2.82%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	2 / 71 (2.82%)	3 / 71 (4.23%)	
occurrences (all)	2	3	
Muscle Spasms			

subjects affected / exposed	4 / 71 (5.63%)	1 / 71 (1.41%)	
occurrences (all)	4	2	
Pain in Extremity			
subjects affected / exposed	1 / 71 (1.41%)	4 / 71 (5.63%)	
occurrences (all)	1	5	
Neck Pain			
subjects affected / exposed	0 / 71 (0.00%)	3 / 71 (4.23%)	
occurrences (all)	0	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 71 (5.63%)	2 / 71 (2.82%)	
occurrences (all)	4	2	
Conjunctivitis			
subjects affected / exposed	2 / 71 (2.82%)	0 / 71 (0.00%)	
occurrences (all)	3	0	
Lower Respiratory Tract Infection			
subjects affected / exposed	2 / 71 (2.82%)	0 / 71 (0.00%)	
occurrences (all)	4	0	
Nasopharyngitis			
subjects affected / exposed	4 / 71 (5.63%)	1 / 71 (1.41%)	
occurrences (all)	4	1	
Pneumonia			
subjects affected / exposed	2 / 71 (2.82%)	5 / 71 (7.04%)	
occurrences (all)	2	5	
Respiratory Tract Infection Viral			
subjects affected / exposed	2 / 71 (2.82%)	2 / 71 (2.82%)	
occurrences (all)	3	2	
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 71 (2.82%)	4 / 71 (5.63%)	
occurrences (all)	2	5	
Urinary Tract Infection			
subjects affected / exposed	2 / 71 (2.82%)	5 / 71 (7.04%)	
occurrences (all)	2	8	
Viral Upper Respiratory Tract Infection			

subjects affected / exposed	2 / 71 (2.82%)	0 / 71 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 71 (1.41%)	2 / 71 (2.82%)	
occurrences (all)	1	2	
Fluid Retention			
subjects affected / exposed	2 / 71 (2.82%)	1 / 71 (1.41%)	
occurrences (all)	2	1	
Gout			
subjects affected / exposed	6 / 71 (8.45%)	2 / 71 (2.82%)	
occurrences (all)	6	2	
Hyperkalaemia			
subjects affected / exposed	3 / 71 (4.23%)	4 / 71 (5.63%)	
occurrences (all)	4	4	
Hyperuricaemia			
subjects affected / exposed	2 / 71 (2.82%)	2 / 71 (2.82%)	
occurrences (all)	2	2	
Hypokalaemia			
subjects affected / exposed	3 / 71 (4.23%)	3 / 71 (4.23%)	
occurrences (all)	3	3	
Hypomagnesaemia			
subjects affected / exposed	1 / 71 (1.41%)	2 / 71 (2.82%)	
occurrences (all)	2	2	
Iron Deficiency			
subjects affected / exposed	2 / 71 (2.82%)	0 / 71 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 February 2017	The overall reason for the amendment 1 was implementation of additional safety monitoring measures after first dose of macitentan, as requested by the Food and Drug Administration (FDA).
12 April 2017	The overall reason for the amendment 2 was addition of medications mainly transported by breast-cancer resistant protein to the list of forbidden medications, as requested by the FDA.
10 April 2018	The overall reason for the amendment 3 was added description of transition to the SERENADE Open-label (OL) extension study, revision of the eligibility and run-in failure criteria, and introduction of a Clinical Event Committee (CEC). Changes made to the statistical methods to allow N-terminal pro-brain natriuretic peptide values measured at screening to be used for stratification at time of treatment assignment and to the definitions of the placebo run-in and macitentan analysis sets.
08 March 2019	The overall reason for the amendment 4 was Addition of the 6-minute walk distance (6MWD) substudy to assess the change in exercise capacity from baseline and removal of the 8-hour safety monitoring period after first dose of macitentan at the start of macitentan run-in. Addition of 2 telephone calls to ensure adequate safety follow-up is established during the run-in phase. Reordered testing hierarchy of the key secondary efficacy endpoints: Kansas City Cardiomyopathy Questionnaire was moved to the first secondary endpoint and accelerometry moved to the second position. Added new hierarchical composite exploratory efficacy endpoint which combined hard (death, hospitalizations) and soft (functional capacity, quality of life) endpoints to allow for a more complete and broader assessment of clinical benefit.
06 February 2020	Overall reason for amendment 5 was early termination of enrollment. Subject recruitment targets not met and completion of study within reasonable timeline not realistic. Updated sample size to reflect early termination of recruitment. Reduced length of double-blind treatment (DBT) period to 24 weeks. Week 24 was pre-defined timepoint to assess primary as well as key secondary endpoints. Secondary endpoint of time to worsening HF event however was planned to be assessed up to Week 52 to gather meaningful information for preparation of pivotal clinical trial development program. Due to reduced sample size, number of worsening HF events was expected to be too low for meaningful analysis of time to worsening HF. DBT period was to be stopped at Week 24, and eligible subjects were to be transitioned to SERENADE OL at that timepoint. Subjects who completed Week 24 visit, were scheduled to come back for an EoT visit within 60 days and enroll in OL study, if eligible. Not all sites participated in OL study. Removed CEC which was appointed to review and adjudicate in blinded fashion worsening HF events, reasons for hospitalization, and causes of death, did not affect safety monitoring and therefore decision was also endorsed by IDMC. DBT period reduced from 52 to 24 weeks, low occurrence of worsening HF events which would not allow for meaningful conclusions to be drawn. Investigator assessment of worsening HF events continued. Re-scheduled accelerometry to be performed 9 consecutive days prior to Week 24 for subjects completing Week 24 to ensure assessment performed on DBT. Stopped sub study assessments (6MWD and Borg Dyspnea Index), due to low count of subjects participating in sub study to allow for meaningful interpretation of results. Planned analysis of sub study data amended to reflect above amendment to protocol. Removed new hierarchical composite exploratory efficacy endpoint that was added in prior amendment due to reduced sample size and stopping of 6MWT sub study.

16 July 2020	Overall reason for amendment 6 was updated the concomitant therapy sections pertaining to new information regarding a drug-drug-interaction of macitentan with moderate dual cytochrome P450 (CYP)3A4 and CYP2C9 inhibitors or co-administration of a combination of moderate CYP3A4 inhibitors and moderate CYP2C9 inhibitors. Data from clinical trials with macitentan 10 mg were reviewed, identifying cases where macitentan 10 mg was administered concomitantly with dual CYP3A4/CYP2C9 inhibitors, such as fluconazole and amiodarone. The review indicated that co-administration of fluconazole or amiodarone with macitentan was not common (between 1% to 3% of subjects). No safety concerns were identified with concurrent administration of fluconazole or amiodarone and macitentan 10 mg.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Recruitment was stopped prematurely in December 2019 due to slow enrollment which resulted in an underpowered study and impacted the meaningful interpretation of the results.

Notes: