Clinical trial results:
Long term, multicenter, single-arm, open-label extension study of the MERIT-1 study, to assess the safety, tolerability and efficacy of macitentan in subjects with inoperable chronic thromboembolic pulmonary hypertension (CTEPH)

Summary

EudraCT number	2013-003457-25
Trial protocol	CZ BE GB HU DE AT NL LT FR
Global end of trial date	21 March 2022

Results information

Result version number	v1 (current)
This version publication date	02 April 2023
First version publication date	02 April 2023

Trial information

Trial identification

Sponsor protocol code	AC-055E202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02060721
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd.
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, 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	21 March 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 March 2022
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 evaluate the long-term safety and tolerability of macitentan 10 milligrams (mg) in subjects with inoperable CTEPH.

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 (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 February 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	Belgium: 1
Country: Number of subjects enrolled	China: 23
Country: Number of subjects enrolled	Czechia: 2
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Russian Federation: 20
Country: Number of subjects enrolled	Thailand: 4
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	Ukraine: 4
Worldwide total number of subjects	76
EEA total number of subjects	18

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)	48
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 76 subjects who completed the double-blind MERIT-1 study, rolled-over to this study (MERIT-2), out of which 38 subjects completed the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Macitentan 10 milligrams (mg)

Arm description:

Eligible subjects who were either randomised to macitentan 10 mg or placebo group during 24 weeks double-blind MERIT-1 (2013-002950-56) study, were rolled-over to this open-label extension study and received macitentan 10 mg tablet orally once daily starting from Day 1 to the end of treatment (treatment exposure ranged from 1 to 82 months).

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

Dosage and administration details:

Macitentan 10 mg tablet was administered orally once daily starting from Day 1 to the end of treatment (treatment exposure ranged from 1 to 82 months).

Number of subjects in period 1	Macitentan 10 milligrams (mg)
Started	76
Completed	38
Not completed	38
Adverse event, serious fatal	14
Physician decision	2
Consent withdrawn by subject	2
Compliance with local regulation: enrolled in China	19
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Macitentan 10 milligrams (mg)

Reporting group description:

Eligible subjects who were either randomised to macitentan 10 mg or placebo group during 24 weeks double-blind MERIT-1 (2013-002950-56) study, were rolled-over to this open-label extension study and received macitentan 10 mg tablet orally once daily starting from Day 1 to the end of treatment (treatment exposure ranged from 1 to 82 months).

Reporting group values	Macitentan 10 milligrams (mg)	Total	
Number of subjects	76	76	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	48	48	
From 65 to 84 years	28	28	
85 years and over	0	0	
Title for AgeContinuous Units: years			
arithmetic mean	57.8		
standard deviation	± 13.99	-	
Title for Gender Units: subjects			
Female	48	48	
Male	28	28	

End points

End points reporting groups

Reporting group title	Macitentan 10 milligrams (mg)

Reporting group description:

Eligible subjects who were either randomised to macitentan 10 mg or placebo group during 24 weeks double-blind MERIT-1 (2013-002950-56) study, were rolled-over to this open-label extension study and received macitentan 10 mg tablet orally once daily starting from Day 1 to the end of treatment (treatment exposure ranged from 1 to 82 months).

Primary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs)[1]

End point description:

An adverse event (AE) is any untoward medical occurrence in a subject participating in a clinical study that does not necessarily have a causal relationship with the pharmaceutical/ biological agent under study. TEAEs are those events that started after administration of the first dose and up to safety follow-up visit/end of study, that is, 30 days after the last dose of study medication. Open-label analysis set (OLAS) included all data from subjects who were enrolled into this open-label extension study, from the time they entered this open-label extension study.

End point type	Primary

End point timeframe:

Up to 30 days after study treatment discontinuation (treatment exposure ranged from 1 to 82 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were reported. No inferential statistics was planned.

End point values	Macitentan 10 milligrams (mg)			
Subject group type	Reporting group			
Number of subjects analysed	76			
Units: Subjects	72			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With AEs Leading to Study Drug Discontinuation

End point title	Number of Subjects With AEs Leading to Study Drug Discontinuation[2]

End point description:

Number of subjects with AEs leading to study drug discontinuation was reported. OLAS included all data from subjects who were enrolled into this open-label extension study, from the time they entered this open-label extension study.

End point type	Primary

End point timeframe:

Up to 30 days after study treatment discontinuation (treatment exposure ranged from 1 to 82 months)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were reported. No inferential statistics was planned.

End point values	Macitentan 10 milligrams (mg)			
Subject group type	Reporting group			
Number of subjects analysed	76			
Units: Subjects	9			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment-emergent Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-emergent Serious Adverse Events (SAEs)[3]

End point description:

A serious adverse event (SAE) is any untoward medical occurrence that at any dose resulting in any of following outcomes: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a suspected transmission of any infectious agent via a medicinal product. Treatment-emergent SAEs were those events that started after administration of the first dose and up to safety follow-up visit/end of study, that is, 30 days after the last dose of study medication. OLAS included all data from subjects who were enrolled into this open-label extension study, from the time they entered this open-label extension study.

End point type	Primary

End point timeframe:

Up to 30 days after study treatment discontinuation (treatment exposure ranged from 1 to 82 months)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were reported. No inferential statistics was planned.

End point values	Macitentan 10 milligrams (mg)			
Subject group type	Reporting group			
Number of subjects analysed	76			
Units: Subjects	44			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Hemoglobin Abnormalities

End point title	Number of Subjects With Hemoglobin Abnormalities[4]

End point description:

Number of subjects with hemoglobin abnormalities were reported. It included hemoglobin less than (<) 80 grams per litre (g/L), hemoglobin <100 g/L, hemoglobin greater than or equal to (>=) 80 g/L and <100 g/L, hemoglobin <100g/L and a decrease of >20 g/L from baseline, decrease of >20 g/L in hemoglobin from baseline, decrease of >20 g/L and <=50 g/L in hemoglobin from baseline, and decrease of >50 g/L in hemoglobin from baseline. OLAS included all data from subjects who were enrolled into this open-label extension study, from the time they entered this open-label extension study.

End point type	Primary

End point timeframe:

Up to 30 days after study treatment discontinuation (treatment exposure ranged from 1 to 82 months)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were reported. No inferential statistics was planned.

End point values	Macitentan 10 milligrams (mg)			
Subject group type	Reporting group			
Number of subjects analysed	76			
Units: Subjects				
Hemoglobin < 80 g/L	0			
Hemoglobin <100 g/L	7			
Hemoglobin >= 80 g/L and <100 g/L	7			
<100 g/L and a decrease from baseline >20 g/L	6			
Decrease of >20 g/L in hemoglobin from baseline	32			
Decrease of >20 g/L and <=50 g/L from baseline	31			
Decrease of >50 g/L in hemoglobin from baseline	5			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Liver Tests Abnormalities

End point title	Number of Subjects With Liver Tests Abnormalities[5]

End point description:

Number of subjects with liver tests abnormalities were reported. It included alanine aminotransferase (ALT) or aspartate aminotransferase (AST): >=3 x Upper limit of the normal range (ULN), >=3 and <5 x ULN, >=5 ULN, and >=5 and <8 x ULN, >= 8 x ULN, and total bilirubin >=2 x ULN. OLAS included all data from subjects who were enrolled into this open-label extension study, from the time they entered this open-label extension study.

End point type	Primary

End point timeframe:

Up to 30 days after study treatment discontinuation (treatment exposure ranged from 1 to 82 months)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were reported. No inferential statistics was planned.

End point values	Macitentan 10 milligrams (mg)			
Subject group type	Reporting group			
Number of subjects analysed	76			
Units: Subjects				
ALT or AST >=3 x ULN	2			
ALT or AST >=3 and <5 x ULN	1			
ALT or AST >=5 x ULN	1			
ALT or AST >=5 and <8 x ULN	0			
ALT or AST >=8 x ULN	1			
Total Bilirubin >=2 x ULN	8			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Blood Pressure at Month 6

End point title	Change from Baseline in Blood Pressure at Month 6[6]

End point description:

Change from baseline in blood pressure (both systolic blood pressure [SBP] and diastolic blood pressure [DBP]) at Month 6 was reported. OLAS included all data from subjects who were enrolled into this open-label extension study, from the time they entered this open-label extension study. Here, 'N' (number of subjects analysed) signifies subjects evaluated for this endpoint.

End point type	Primary

End point timeframe:

Baseline and Month 6

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were reported. No inferential statistics was planned.

End point values	Macitentan 10 milligrams (mg)			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: Millimetres of mercury (mmHg)				
arithmetic mean (standard deviation)				
SBP	-0.4 (± 13.15)			
DBP	-2.8 (± 9.51)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Pulse Rate at Month 6

End point title	Change from Baseline in Pulse Rate at Month 6[7]

End point description:

Change from baseline in pulse rate at Month 6 was reported. OLAS included all data from subjects who were enrolled into this open-label extension study, from the time they entered this open-label extension study. Here, 'N' (number of subjects analysed) signifies subjects evaluated for this endpoint.

End point type	Primary

End point timeframe:

Baseline and Month 6

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were reported. No inferential statistics was planned.

End point values	Macitentan 10 milligrams (mg)			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: Beats per minute				
arithmetic mean (standard deviation)	-1.1 (± 8.76)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Body Weight at Month 6

End point title	Change from Baseline in Body Weight at Month 6[8]

End point description:

Change from baseline in body weight at Month 6 was reported. OLAS included all data from subjects who were enrolled into this open-label extension study, from the time they entered this open-label extension study. Here, 'N' (number of subjects analysed) signifies subjects evaluated for this endpoint.

End point type	Primary

End point timeframe:

Baseline and Month 6

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were reported. No inferential statistics was planned.

End point values	Macitentan 10 milligrams (mg)			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: kilograms (kg)				
arithmetic mean (standard deviation)	-0.35 (± 2.871)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 30 days after study treatment discontinuation (treatment exposure ranged from 1 to 82 months)

Adverse event reporting additional description:

Open-label analysis set (OLAS) included all data from subjects who were enrolled into this open-label extension study, from the time they entered this open-label extension study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Macitentan 10 milligrams (mg)

Reporting group description:

Eligible subjects who were either randomised to macitentan 10 mg or placebo group during 24 weeks double-blind MERIT-1 (2013-002950-56) study, were rolled-over to this open-label extension study and received macitentan 10 mg tablet orally once daily starting from Day 1 to the end of treatment (treatment exposure ranged from 1 to 82 months).

Serious adverse events	Macitentan 10 milligrams (mg)		
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 76 (57.89%)		
number of deaths (all causes)	14		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast Cancer			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric Cancer Stage Iv			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast Cancer Metastatic			

subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Air Embolism			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reperfusion Injury			
subjects affected / exposed	2 / 76 (2.63%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Angioplasty			
subjects affected / exposed	3 / 76 (3.95%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		
Arterial Angioplasty			
subjects affected / exposed	7 / 76 (9.21%)		
occurrences causally related to treatment / all	0 / 23		
deaths causally related to treatment / all	0 / 0		
Pulmonary Endarterectomy			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	3 / 76 (3.95%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		

General Physical Health Deterioration				
subjects affected / exposed	2 / 76 (2.63%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Peripheral Swelling				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Multiple Organ Dysfunction Syndrome				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pyrexia				
subjects affected / exposed	2 / 76 (2.63%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute Respiratory Failure				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Asthma				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	2 / 76 (2.63%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	2 / 76 (2.63%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			

Hypercapnia				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Obstructive Airways Disorder				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pickwickian Syndrome				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary Embolism				
subjects affected / exposed	3 / 76 (3.95%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 2			
Sleep Apnoea Syndrome				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary Hypertension				
subjects affected / exposed	6 / 76 (7.89%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 1			
Investigations				
Catheterisation Cardiac				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chest X-Ray Abnormal				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoglobin Decreased				

subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Head Injury				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Fall				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Chemical Burns of Eye				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lumbar Vertebral Fracture				
subjects affected / exposed	3 / 76 (3.95%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Arteriovenous Malformation				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute Myocardial Infarction				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Angina Pectoris				

subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aortic Valve Stenosis				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial Fibrillation				
subjects affected / exposed	2 / 76 (2.63%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Atrial Flutter				
subjects affected / exposed	2 / 76 (2.63%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Atrial Tachycardia				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac Arrest				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac Failure				
subjects affected / exposed	4 / 76 (5.26%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 3			
Right Ventricular Failure				
subjects affected / exposed	5 / 76 (6.58%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 2			
Coronary Artery Disease				

subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac Failure Congestive			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac Failure Acute			
subjects affected / exposed	3 / 76 (3.95%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Nervous system disorders			
Haemorrhage Intracranial			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Diplegia			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Deafness Neurosensory			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vision Blurred			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastric Polyps			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal Motility Disorder			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis Acute			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large Intestine Polyp			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritoneal Adhesions			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal Failure			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Systemic Lupus Erythematosus			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendiceal Abscess			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Covid-19 Pneumonia			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia Parainfluenzae Viral			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	4 / 76 (5.26%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Neutropenic Sepsis				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pulmonary Tuberculosis				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis Acute				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis Chronic				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory Tract Infection				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Sepsis				
subjects affected / exposed	2 / 76 (2.63%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Septic Shock				
subjects affected / exposed	2 / 76 (2.63%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Streptococcal Sepsis				

subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Macitentan 10 milligrams (mg)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 76 (88.16%)		
Investigations			
Blood Bilirubin Increased			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	6		
Blood Creatinine Increased			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	4		
C-Reactive Protein Increased			
subjects affected / exposed	6 / 76 (7.89%)		
occurrences (all)	6		
Haemoglobin Decreased			
subjects affected / exposed	13 / 76 (17.11%)		
occurrences (all)	17		
Weight Decreased			
subjects affected / exposed	7 / 76 (9.21%)		
occurrences (all)	8		
Cardiac disorders			
Cardiac Failure			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	5		
Nervous system disorders			

Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Syncope subjects affected / exposed occurrences (all)	7 / 76 (9.21%) 10 8 / 76 (10.53%) 15 7 / 76 (9.21%) 8		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	10 / 76 (13.16%) 11		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) Oedema Peripheral subjects affected / exposed occurrences (all)	4 / 76 (5.26%) 5 11 / 76 (14.47%) 13		
Eye disorders Cataract subjects affected / exposed occurrences (all)	6 / 76 (7.89%) 7		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	7 / 76 (9.21%) 11		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Haemoptysis subjects affected / exposed occurrences (all) Dyspnoea	9 / 76 (11.84%) 11 4 / 76 (5.26%) 7		

subjects affected / exposed	7 / 76 (9.21%)		
occurrences (all)	7		
Pulmonary Hypertension			
subjects affected / exposed	11 / 76 (14.47%)		
occurrences (all)	12		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	5		
Back Pain			
subjects affected / exposed	7 / 76 (9.21%)		
occurrences (all)	7		
Arthralgia			
subjects affected / exposed	6 / 76 (7.89%)		
occurrences (all)	9		
Pain in Extremity			
subjects affected / exposed	6 / 76 (7.89%)		
occurrences (all)	6		
Infections and infestations			
Bronchitis			
subjects affected / exposed	9 / 76 (11.84%)		
occurrences (all)	14		
Respiratory Tract Infection Viral			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	4		
Nasopharyngitis			
subjects affected / exposed	9 / 76 (11.84%)		
occurrences (all)	15		
Covid-19			
subjects affected / exposed	6 / 76 (7.89%)		
occurrences (all)	7		
Urinary Tract Infection			
subjects affected / exposed	7 / 76 (9.21%)		
occurrences (all)	14		
Upper Respiratory Tract Infection			

subjects affected / exposed occurrences (all)	12 / 76 (15.79%) 21		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all) Hyperuricaemia subjects affected / exposed occurrences (all)	 4 / 76 (5.26%) 8 4 / 76 (5.26%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2020	The purpose of this amendment was to update the study specific criteria for drug interruption/ permanent discontinuation and forbidden concomitant medication sections to prohibit strong Cytochrome P-450 (CYP) 3A4 inhibitors, moderate dual CYP3A4/CYP2C9 inhibitors, and concomitant administration of moderate CYP3A4 and CYP2C9 inhibitors.
28 September 2020	The purpose of this amendment was to update the description of the investigational medicinal product used in this study from debossed on one side to debossed on either one or both sides.
22 June 2021	The purpose of this amendment was to clarify how to manage the roll-over of MERIT-2 subjects into a continued access program (post-trial access program or other open-label extension study). In addition, the forbidden concomitant medications section was updated to clarify that macitentan 10 mg is not considered as an investigational treatment.

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.

Study limitations included the open-label (OL), uncontrolled design, and small sample size.

Notes: