Clinical trial results:
mUlticenter, single-arM, open-laBel, long-teRm safety study with macitEntan in patients with puLmonary hypertension previousLy treated with mAcitentan in clinical studies UMBRELLA

Summary

EudraCT number	2017-003934-10
Trial protocol	FR PL BE
Global end of trial date	27 December 2023

Results information

Result version number	v1 (current)
This version publication date	03 January 2025
First version publication date	03 January 2025

Trial information

Trial identification

Sponsor protocol code	AC-055-314

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03422328
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	27 December 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of this trial was to investigate the long-term safety of macitentan 10 milligrams in subjects with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 May 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	50 Months
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	Belarus: 6
Country: Number of subjects enrolled	France: 120
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Türkiye: 2
Country: Number of subjects enrolled	Ukraine: 3
Worldwide total number of subjects	147
EEA total number of subjects	124

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)	1
Adults (18-64 years)	100
From 65 to 84 years	46
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 147 subjects were enrolled and treated in this study, out of which 90 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:

Subjects with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) who received macitentan therapy in their parent studies (NCT00667823, NCT02112487, NCT02310672, NCT02968901, NCT02558231, NCT02382016, and NCT02060721) were enrolled and received macitentan 10 mg tablet orally once daily from Day 1 up to 49.7 months. Subjects were then followed up for safety up to 30 days after the last dose of study treatment.

Arm type	Experimental
Investigational medicinal product name	Macitentan 10 mg
Investigational medicinal product code	
Other name	JNJ-67896062; ACT-064992
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received macitentan 10 mg orally once daily from Day 1 up to 49.7 months.

Number of subjects in period 1	Macitentan 10 milligrams (mg)
Started	147
Completed	90
Not completed	57
Physician decision	26
Consent withdrawn by subject	6
Deaths	25

Baseline characteristics

Reporting groups	
Reporting group title	Macitentan 10 milligrams (mg)

Reporting group description:

Subjects with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) who received macitentan therapy in their parent studies (NCT00667823, NCT02112487, NCT02310672, NCT02968901, NCT02558231, NCT02382016, and NCT02060721) were enrolled and received macitentan 10 mg tablet orally once daily from Day 1 up to 49.7 months. Subjects were then followed up for safety up to 30 days after the last dose of study treatment.

Reporting group values	Macitentan 10 milligrams (mg)	Total	
Number of subjects	147	147	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	100	100	
From 65 to 84 years	46	46	
85 years and over	0	0	
Title for AgeContinuous Units: years			
arithmetic mean	58.8		
standard deviation	± 13.67	-	
Title for Gender Units: subjects			
Female	98	98	
Male	49	49	

End points

End points reporting groups

Reporting group title	Macitentan 10 milligrams (mg)

Reporting group description:

Subjects with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) who received macitentan therapy in their parent studies (NCT00667823, NCT02112487, NCT02310672, NCT02968901, NCT02558231, NCT02382016, and NCT02060721) were enrolled and received macitentan 10 mg tablet orally once daily from Day 1 up to 49.7 months. Subjects were then followed up for safety up to 30 days after the last dose of study treatment.

Primary: Exposure Adjusted Incidence Rate of Treatment-emergent Adverse Events (TEAEs) per 100 Person-years (PY)

End point title	Exposure Adjusted Incidence Rate of Treatment-emergent Adverse Events (TEAEs) per 100 Person-years (PY)[1]

End point description:

The exposure adjusted incidence rate of TEAE per 100 PY was calculated as the number of subjects who had TEAEs during the study after the first dose of study drug divided by the sum of all subjects years (where a year was 365.25 days) of follow-up while at risk of TEAE during the study. An adverse event (AE) was any untoward medical occurrence in a clinical study subject administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the study treatment. TEAEs were those AEs with onset date from signature of informed consent (IC) until 30 days after the last dose of macitentan except for subjects entering a continued access program for whom TEAEs were those AEs with onset date from signature of IC until end of study treatment. The safety analysis set included all subjects who had signed the IC.

End point type	Primary

End point timeframe:

From Day 1 up to 30 days after last dose of study drug (up to 50.7 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 data was planned to be reported for this endpoint.

End point values	Macitentan 10 milligrams (mg)			
Subject group type	Reporting group			
Number of subjects analysed	147			
Units: TEAEs per 100 PY				
number (confidence interval 95%)	41.44 (34.43 to 49.87)			

Statistical analyses

No statistical analyses for this end point

Primary: Exposure Adjusted Incidence Rate of Treatment-emergent Serious Adverse Events (TESAEs) per 100 PY

End point title	Exposure Adjusted Incidence Rate of Treatment-emergent Serious Adverse Events (TESAEs) per 100 PY[2]

End point description:

Exposure adjusted incidence rate of TESAE per 100 PY was calculated as number of subjects who had TESAEs during the study after the first dose of study drug divided by the sum of all subjects' years (where a year was 365.25 days) of follow-up while at risk of TESAE during the study. TEAEs were those AEs with onset date from signature of IC until 30 days after last dose of macitentan except for subjects entering a continued access program for whom TEAEs were those AEs with onset date from signature of IC until end of study treatment. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalisation; life-threatening experience (immediately result in death); persistent or significant disability/incapacity; congenital anomaly/birth defect; suspected transmission of any infectious agent via a medicinal product or medically important. Safety analysis set included all subjects who had signed the IC.

End point type	Primary

End point timeframe:

From Day 1 up to 30 days after last dose of study drug (up to 50.7 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 data was planned to be reported for this endpoint.

End point values	Macitentan 10 milligrams (mg)			
Subject group type	Reporting group			
Number of subjects analysed	147			
Units: TESAEs per 100 PY				
number (confidence interval 95%)	20.56 (16.24 to 26.03)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Abnormal Pregnancy Outcomes With Maternal Exposure to Macitentan

End point title	Number of Subjects With Abnormal Pregnancy Outcomes With Maternal Exposure to Macitentan[3]

End point description:

Number of subjects with abnormal pregnancy outcomes with maternal exposure to macitentan was reported. Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancies) wre considered SAEs and must be reported using a SAE reporting form. Any subject who becomes pregnant during the study must discontinue further study treatment. The safety set included all subjects who had signed the IC.

End point type	Primary

End point timeframe:

From Day 1 up to 30 days after last dose of study drug (up to 50.7 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 data was planned to be reported for this endpoint.

End point values	Macitentan 10 milligrams (mg)			
Subject group type	Reporting group			
Number of subjects analysed	147			
Units: Subjects	0			

Statistical analyses

No statistical analyses for this end point

Primary: Treatment Exposure Adjusted Incidence Rate of TEAEs Leading to Discontinuation of Study Treatment per 100 PY

End point title	Treatment Exposure Adjusted Incidence Rate of TEAEs Leading to Discontinuation of Study Treatment per 100 PY[4]

End point description:

Exposure adjusted incidence rate of TEAE leading to discontinuation of study treatment per 100 PY was calculated as number of subjects who had TEAEs leading to discontinuation of study treatment during study after first dose of study drug divided by sum of all subjects years (where a year was 365.25 days) of follow-up while at risk of TEAE during the study. An AE was any untoward medical occurrence in a clinical study subject administered a pharmaceutical (investigational or non-investigational) product. TEAEs were those AEs with onset date from signature of IC until 30 days after last dose of macitentan except for subjects entering a continued access program for whom TEAEs were those AEs with onset date from signature of IC until end of study treatment. Any AE was recorded that leads to premature discontinuation of study treatment and decision may be made by the subject, investigator or sponsor. Safety analysis set included all subjects who had signed the IC.

End point type	Primary

End point timeframe:

From Day 1 up to 30 days after last dose of study drug (up to 50.7 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 data was planned to be reported for this endpoint.

End point values	Macitentan 10 milligrams (mg)			
Subject group type	Reporting group			
Number of subjects analysed	147			
Units: TEAEs leading to discontinuation/100PY				
number (confidence interval 95%)	1.84 (0.92 to 3.68)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Day 1 up to 30 days after last dose of study drug (up to 50.7 months)	
Adverse event reporting additional description:	
The safety analysis set included all subject who had signed the informed consent.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups	
Reporting group title	Macitentan 10 mg
Reporting group description:	
Subjects with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) who received macitentan therapy in their parent studies (NCT00667823, NCT02112487, NCT02310672, NCT02968901, NCT02558231, NCT02382016, and NCT02060721) were enrolled and received macitentan 10 mg tablet orally once daily from Day 1 up to 49.7 months. Subjects were then followed up for safety up to 30 days after the last dose of study treatment.	

Serious adverse events	Macitentan 10 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	69 / 147 (46.94%)		
number of deaths (all causes)	25		
number of deaths resulting from adverse events	25		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bone Cancer			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Glioblastoma			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast Cancer			
subjects affected / exposed	4 / 147 (2.72%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Cholangiocarcinoma			

subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gallbladder Cancer				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric Cancer				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Squamous Cell Carcinoma of the Hypopharynx				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Squamous Cell Carcinoma of Pharynx				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small Cell Lung Cancer				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Renal Neoplasm				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate Cancer				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal Squamous Cell Carcinoma				

subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malignant Neoplasm Progression				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Lung Adenocarcinoma				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Vascular disorders				
Raynaud's Phenomenon				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Appendicectomy				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial Septal Defect Repair				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Catheterisation Venous				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour Ablation				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung Transplant				

subjects affected / exposed	2 / 147 (1.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Inguinal Hernia Repair				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatectomy				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Drug Therapy				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystectomy				
subjects affected / exposed	2 / 147 (1.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
General Physical Health Deterioration				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	2 / 147 (1.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Cyst				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema Peripheral				

subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Puncture Site Haematoma			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sudden Death			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	3 / 147 (2.04%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Pulmonary Arterial Hypertension			
subjects affected / exposed	10 / 147 (6.80%)		
occurrences causally related to treatment / all	0 / 12		
deaths causally related to treatment / all	0 / 4		
Pulmonary Artery Aneurysm			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Pulmonary Embolism			
subjects affected / exposed	2 / 147 (1.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Respiratory Failure			
subjects affected / exposed	3 / 147 (2.04%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Cardiovascular Somatic Symptom Disorder			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Alcohol Withdrawal Syndrome			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device Malfunction			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic Enzyme Increased			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Weight Decreased			

subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular Resistance Pulmonary Increased				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Brain Contusion				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Craniocerebral Injury				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fat Embolism				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Femur Fracture				
subjects affected / exposed	2 / 147 (1.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Shoulder Fracture				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Spinal Fracture				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subdural Haematoma				

subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	2 / 147 (1.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac Arrest			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Atrial Fibrillation			
subjects affected / exposed	2 / 147 (1.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Arrhythmia Supraventricular			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arrhythmia			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac Failure			
subjects affected / exposed	4 / 147 (2.72%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Myocardial Infarction			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Cardiopulmonary Failure			

subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac Failure Acute				
subjects affected / exposed	2 / 147 (1.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Cardiac Tamponade				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardio-Respiratory Arrest				
subjects affected / exposed	2 / 147 (1.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Pericardial Effusion				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Right Ventricular Failure				
subjects affected / exposed	9 / 147 (6.12%)			
occurrences causally related to treatment / all	0 / 13			
deaths causally related to treatment / all	0 / 3			
Tachycardia				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Brain Compression				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral Haemorrhage				

subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Syncope			
subjects affected / exposed	4 / 147 (2.72%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Hepatic Encephalopathy			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic Stroke			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	4 / 147 (2.72%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Acute Abdomen			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal Pain			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			

subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Rectal Haemorrhage				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Gastrointestinal Haemorrhage				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute Kidney Injury				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Sjogren's Syndrome				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neck Pain				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Back Pain				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Arthritis Bacterial				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Covid-19			
subjects affected / exposed	2 / 147 (1.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Device Related Infection			
subjects affected / exposed	2 / 147 (1.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocarditis			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia Bacterial			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	5 / 147 (3.40%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			

subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ear, Nose and Throat Infection				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Streptococcal Infection				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Suspected Covid-19				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Gout				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fluid Retention				
subjects affected / exposed	1 / 147 (0.68%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Diabetic Metabolic Decompensation				
subjects affected / exposed	1 / 147 (0.68%)			
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 mg		
Total subjects affected by non-serious adverse events subjects affected / exposed	18 / 147 (12.24%)		
Infections and infestations Covid-19 subjects affected / exposed occurrences (all)	18 / 147 (12.24%) 19		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 March 2018	This amendment was planned for exclusion criterion 1 was relaxed to include subjects with hemoglobin lower than 80 grams per litre (g/L), with treatment starting as soon as hemoglobin was higher than 80 g/L.
06 June 2018	This amendment was planned to include the list of parent studies was expanded to include patients who were treated with macitentan in study AC-055-404 (PORTICO).
03 December 2018	This amendment was panned to include the all adverse events (AEs) and serious AEs (SAEs) leading to permanent discontinuation of study treatment must be reported to Actelion drug safety. Laboratory results within 7 days prior to Visit 1 were acceptable for eligibility assessment. Concomitant therapies no longer need to be documented in the case report form (CRF). For patients temporarily ineligible for UMBRELLA at the end of the parent study, an interruption of macitentan treatment was acceptable if not longer than 4 weeks.
23 January 2019	This amendment was planned to include the inclusion of patients exiting from SERAPHIN OL in additional European countries, Asia and in Latin America, who do not have access to reimbursed macitentan in their country. The number of patients and sites was updated. References to France/French were generalized to cover affected regions. Changes were made on the study medication bottle labels. The definitions of the full analysis set and safety set were clarified. It was clarified that Actelion could decide to terminate the study at country or site level.
17 July 2020	This amendment was planned to include exclusion criterion 8 was added to exclude subjects who, were currently receiving treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor. A new section (5.1.10.3) was introduced to add the treatment with moderate dual CYP3A4/cytochrome P450 family 2 subfamily C member 9 (CYP2C9) inhibitors or coadministration of moderate CYP3A4- and moderate CYP2C9 inhibitors to the list of "Study-specific criteria for interruption/premature discontinuation of study treatment". Section 5.2.5 was modified to include new information on concomitant administration of CYP34A and CYP2C9 inhibitors was added. A new reference (Food and Drug Administration 2020) was added to the reference list and Section 5.2.5.
15 October 2020	This amendment was planned to include the long term data of macitentan in subjects with pulmonary arterial hypertension (PAH) and MERIT-1 studies have been updated. These data show that subjects with chronic thromboembolic pulmonary hypertension (CTEPH) can be included in this study in addition to the PAH subjects; therefore, the primary objective of the study was updated to also includes subjects with CTEPH and allow subjects rolling over from the MERIT-2 open-label study in European and Asian countries where access to a post-trial program was not available. In addition, the food and drug administration (FDA) post marketing requirement to assess serious hepatic AEs of interest by an Independent Liver Safety Data Review Board (ILSDRB) was fulfilled in September 2019 and consequently, mention to ILSDRB was removed. Moreover, the purpose of this amendment was to adapt internal safety reporting processes, clarify the Child-Pugh assessments as needed for exclusion criterion 3, make minor corrections, and perform editorial document formatting revisions.
05 August 2021	This amendment was planned for to clarify how to manage the roll-over of UMBRELLA subjects into a continued access program (post-trial access [PTA] program or other open-label extension study). Also the number of subjects and sites was revised.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported