Clinical trial results:
A Prospective, Randomized, Double-Blind, Multicenter, Placebo-Controlled, Parallel Group, Adaptive Phase 3 Study with Open-Label Extension to Evaluate Efficacy and Safety of Macitentan 75 mg in Inoperable or Persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension

Summary

EudraCT number	2019-004131-24
Trial protocol	CZ DE GB HU PL ES AT SK LT FR IT PT DK
Global end of trial date	20 December 2023

Results information

Result version number	v1 (current)
This version publication date	05 January 2025
First version publication date	05 January 2025

Trial information

Trial identification

Sponsor protocol code	67896062CTP3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04271475
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd
Sponsor organisation address	16 Gewerbestrasse, 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	20 December 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 December 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to evaluate the effect of macitentan 75 milligrams (mg) versus placebo on exercise capacity at Week 28 in subjects with chronic thromboembolic pulmonary hypertension (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 Practice and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 July 2020
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	Singapore: 1
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 13
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Lithuania: 1
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Türkiye: 6
Country: Number of subjects enrolled	Taiwan: 2

Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	China: 17
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Japan: 14
Country: Number of subjects enrolled	Korea, Republic of: 8
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Saudi Arabia: 2
Country: Number of subjects enrolled	Thailand: 2
Worldwide total number of subjects	127
EEA total number of subjects	47

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)	56
From 65 to 84 years	71
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Study comprised of screening, double-blind (DB), open-label (OL) and safety follow-up (FU) periods. The DB period started with an 8-week up-titration phase and lasted until all subjects either completed the Week 28 visit or prematurely discontinued the study.

Period 1

Period 1 title	DB Period: Day 1 up to EODBT
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Double blind

Arms

Are arms mutually exclusive?	Yes
Arm title	Double Blind (DB) Period: Macitentan

Arm description:

During the 8-week up-titration phase, subjects received macitentan doses orally once daily (QD): 10 mg tablet for 4 weeks followed by 37.5 mg tablet for another 4 weeks prior to reaching the target maintenance phase dose of macitentan 75 mg QD. Subjects were to remain on double-blind maintenance treatment until the last subject randomised completed the Week 28 visit. Subjects who prematurely discontinued DB study treatment prior to Week 28 but did not withdraw consent were asked to enter post-treatment observation period (PTOP) from DB period last dose until Week 28. Median exposure to DB treatment was 24.50 weeks (minimum: 3.9 weeks; maximum: 160.4 weeks).

Arm type	Experimental
Investigational medicinal product name	Macitentan
Investigational medicinal product code	ACT-064992
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received macitentan 10 mg QD for 4 weeks followed by macitentan 37.5 mg QD for another 4 weeks during the up-titration phase, prior to reaching the target maintenance dose of macitentan 75 mg QD. Subject remained on DB maintenance treatment until the last subject randomised completed the Week 28 visit.

Arm title	DB Period: Placebo

Arm description:

Subjects received placebo matched to macitentan dose levels during the DB treatment period. Subjects who prematurely discontinued DB study treatment prior to Week 28 but did not withdraw consent were asked to enter PTOP from DB period last dose until Week 28. Median exposure to DB treatment was 44 weeks (minimum: 4 weeks; maximum: 147.9 weeks).

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:

Subjects received placebo matched to macitentan dose levels during the DB treatment period.

Number of subjects in period 1	Double Blind (DB) Period: Macitentan	DB Period: Placebo
Started	64	63
Completed	1	1
Not completed	63	62
Adverse event, serious fatal	1	-
Physician decision	8	1
Consent withdrawn by subject	5	4
Study terminated by sponsor	41	52
Unspecified	8	5

Period 2

Period 2 title	OL Period:Day 1 upto End of OL Treatment
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Open Label (OL) Period: DB Macitentan

Arm description:

Subjects who were treated with macitentan in the DB period and had reached the target dose of macitentan 75 mg and completed the DB period as per protocol were considered eligible to transition into the 104-week OL period and they continued macitentan 75 mg tablet orally QD from end of double blind treatment (EODBT) until study termination. Subjects who experienced a clinical worsening event confirmed by the clinical event committee (CEC), were allowed to transition to the OL period at any time after Week 28. Median exposure to OL treatment was 72 weeks (minimum: 8.1 weeks; maximum: 84.6 weeks).

Arm type	Experimental
Investigational medicinal product name	Macitentan
Investigational medicinal product code	ACT-064992
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects continued macitentan 75 mg QD from EODBT until study termination.

Arm title	OL Period: DB Placebo

Arm description:

Subjects who were treated with placebo in the DB period and had completed the DB period as per protocol were considered eligible to transition into the 104-week OL period and were up-titrated to the target dose of macitentan 75 mg (macitentan 10 mg for 4 weeks, followed by macitentan 37.5 mg for another 4 weeks). Subjects who experienced a clinical worsening event confirmed by the CEC, were allowed to transition to the OL period at any time after Week 28. Median exposure to OL treatment was 72 weeks (minimum: 8.1 weeks; maximum: 84.6 weeks).

Arm type	Experimental
Investigational medicinal product name	Macitentan
Investigational medicinal product code	ACT-064992
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were up-titrated to the target dose of macitentan 75 mg (macitentan 10 mg for 4 weeks, followed by macitentan 37.5 mg for another 4 weeks).

Number of subjects in period 2	Open Label (OL) Period: DB Macitentan	OL Period: DB Placebo
Started	1	1
Completed	0	0
Not completed	1	1
Study terminated by sponsor	1	-
Unspecified	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Double Blind (DB) Period: Macitentan
Reporting group description:	
During the 8-week up-titration phase, subjects received macitentan doses orally once daily (QD): 10 mg tablet for 4 weeks followed by 37.5 mg tablet for another 4 weeks prior to reaching the target maintenance phase dose of macitentan 75 mg QD. Subjects were to remain on double-blind maintenance treatment until the last subject randomised completed the Week 28 visit. Subjects who prematurely discontinued DB study treatment prior to Week 28 but did not withdraw consent were asked to enter post-treatment observation period (PTOP) from DB period last dose until Week 28. Median exposure to DB treatment was 24.50 weeks (minimum: 3.9 weeks; maximum: 160.4 weeks).	
Reporting group title	DB Period: Placebo
Reporting group description:	
Subjects received placebo matched to macitentan dose levels during the DB treatment period. Subjects who prematurely discontinued DB study treatment prior to Week 28 but did not withdraw consent were asked to enter PTOP from DB period last dose until Week 28. Median exposure to DB treatment was 44 weeks (minimum: 4 weeks; maximum: 147.9 weeks).	

Reporting group values	Double Blind (DB) Period: Macitentan	DB Period: Placebo	Total
Number of subjects	64	63	127
Age categorical Units: Subjects			
In Utero	0	0	0
Preterm newborn infants (gestional age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days - 23 months)	0	0	0
Children (2 - 11 years)	0	0	0
12 - 17 years	0	0	0
Adults (18 - 64 years)	23	33	56
From 65 - 84 years	41	30	71
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	64.7	60.3	
standard deviation	± 11.69	± 12.84	-
Gender categorical Units: Subjects			
Male	27	21	48
Female	37	42	79

End points

End points reporting groups

Reporting group title	Double Blind (DB) Period: Macitentan

Reporting group description:

During the 8-week up-titration phase, subjects received macitentan doses orally once daily (QD): 10 mg tablet for 4 weeks followed by 37.5 mg tablet for another 4 weeks prior to reaching the target maintenance phase dose of macitentan 75 mg QD. Subjects were to remain on double-blind maintenance treatment until the last subject randomised completed the Week 28 visit. Subjects who prematurely discontinued DB study treatment prior to Week 28 but did not withdraw consent were asked to enter post-treatment observation period (PTOP) from DB period last dose until Week 28. Median exposure to DB treatment was 24.50 weeks (minimum: 3.9 weeks; maximum: 160.4 weeks).

Reporting group title	DB Period: Placebo

Reporting group description:

Subjects received placebo matched to macitentan dose levels during the DB treatment period. Subjects who prematurely discontinued DB study treatment prior to Week 28 but did not withdraw consent were asked to enter PTOP from DB period last dose until Week 28. Median exposure to DB treatment was 44 weeks (minimum: 4 weeks; maximum: 147.9 weeks).

Reporting group title	Open Label (OL) Period: DB Macitentan

Reporting group description:

Subjects who were treated with macitentan in the DB period and had reached the target dose of macitentan 75 mg and completed the DB period as per protocol were considered eligible to transition into the 104-week OL period and they continued macitentan 75 mg tablet orally QD from end of double blind treatment (EODBT) until study termination. Subjects who experienced a clinical worsening event confirmed by the clinical event committee (CEC), were allowed to transition to the OL period at any time after Week 28. Median exposure to OL treatment was 72 weeks (minimum: 8.1 weeks; maximum: 84.6 weeks).

Reporting group title	OL Period: DB Placebo

Reporting group description:

Subjects who were treated with placebo in the DB period and had completed the DB period as per protocol were considered eligible to transition into the 104-week OL period and were up-titrated to the target dose of macitentan 75 mg (macitentan 10 mg for 4 weeks, followed by macitentan 37.5 mg for another 4 weeks). Subjects who experienced a clinical worsening event confirmed by the CEC, were allowed to transition to the OL period at any time after Week 28. Median exposure to OL treatment was 72 weeks (minimum: 8.1 weeks; maximum: 84.6 weeks).

Primary: Change From Baseline in 6-minute Walk Distance (6MWD) at Week 28

End point title	Change From Baseline in 6-minute Walk Distance (6MWD) at Week 28

End point description:

Change from baseline in 6MWD as measured by 6-minute walk test (6MWT)) at Week 28 was reported. The purpose of the 6MWT was to quantify exercise tolerance and capacity. This standardized test measured the distance an individual was able to walk over a total of six minutes on a hard, flat surface with no obstacles. The goal was for the individual to walk as far as possible in 6 minutes. Full analysis set (FAS) included all randomised subjects assigned to a study intervention and were analysed according to the intervention they had been assigned to via interactive web response system (IWRS). Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this end point.

End point type	Primary

End point timeframe:

Baseline (Day 1), Week 28

End point values	Double Blind (DB) Period: Macitentan	DB Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	48		
Units: Meters				
least squares mean (standard error)	9.7 (± 5.81)	25.8 (± 5.78)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Estimated by mixed model repeated measurements method.	
Comparison groups	DB Period: Placebo v Double Blind (DB) Period: Macitentan
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.974
Method	Mixed model repeated measures
Parameter estimate	Least square mean
Point estimate	-16.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.34
upper limit	0.16
Variability estimate	Standard error of the mean
Dispersion value	8.2

Secondary: Number of Subjects with Improvement in World Health Organisation Functional Class (WHO FC) From Baseline to Week 28

End point title	Number of Subjects with Improvement in World Health Organisation Functional Class (WHO FC) From Baseline to Week 28
End point description: Number of subjects with improvement in WHO FC from baseline to Week 28 were reported. Improvement (decrease) in WHO FC from baseline to Week 28 was calculated for each subject. WHO FC test was used to assess disease severity. Four FC were defined from FC I (no limitation of physical activity) to FC IV (inability to carry out any physical activity without symptoms). For analysis purpose, these WHO FC class values were transformed to a scale with scores ranged from 1 to 4; where a score 1 corresponded to WHO FC Class I and a score 4 corresponded to WHO FC Class IV. The higher scores indicated greater symptom severity or worse impact. Improvement was considered when a subject changed from a higher class to a lower class. FAS: all randomised subjects assigned to a study intervention and were analysed according to the intervention they had been assigned to via IWRS. Here, 'N' (number of subjects analysed) signifies number of subjects evaluable for this endpoint.	
End point type	Secondary
End point timeframe: From Baseline (Day 1) up to Week 28	

End point values	Double Blind (DB) Period: Macitentan	DB Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	43		
Units: Subjects	7	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Time First Clinical Event Committee (CEC) Confirmed to Clinical Worsening up to End-of Double-blind-treatment (EODBT) Period

End point title	Time First Clinical Event Committee (CEC) Confirmed to Clinical Worsening up to End-of Double-blind-treatment (EODBT) Period

End point description:

Time (months) to first CEC-confirmed clinical worsening up to EODBT were reported. Clinical worsening: occurrence of at least 1 of following: 1) All-cause death; 2) Heart and/or lung transplantation; 3) Hospitalization or Deterioration from baseline due to unplanned pulmonary hypertension (PH) identified by at least 1 of following: a) Persistent increase in World Health Organization functional class (WHO FC) that could not be explained by another cause (like viral infection); b) Persistent deterioration by at least 15 percent exercise capacity; (by 6MWD); c) New/worsened signs/symptoms of right heart failure; 5) Rescue pulmonary endarterectomy(PEA) and/or balloon pulmonary angioplasty(BPA) procedure. FAS: randomised subjects assigned to study intervention and were analysed according to received intervention via IWRS. 99999 signifies data could not be calculated due to low number of subjects with events.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to EODBT: median 24.5 weeks [min 3.9 weeks; max 160.4 weeks] for macitentan, median 44 weeks (min 4 weeks; max 147.9 weeks) for placebo

End point values	Double Blind (DB) Period: Macitentan	DB Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	63		
Units: Months				
median (confidence interval 95%)	99999 (19.0 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 28 in Pulmonary Arterial Hypertension - Symptoms and Impact (PAH-SYMPACT) - Cardiopulmonary Symptom Domain Score

End point title	Change From Baseline to Week 28 in Pulmonary Arterial Hypertension - Symptoms and Impact (PAH-SYMPACT) - Cardiopulmonary Symptom Domain Score

End point description:

The cardiopulmonary symptoms domain consisted 6 items: dyspnea, fatigue, lack of energy, swelling in ankles/legs/stomach area and cough, on a scale from 0 no symptom at all) to 4 (very severe symptoms). The symptoms part of the PAH-SYMPACT was administered daily over a 7-day period. The recall period of symptom items was the last 24 hours. An average cardiopulmonary symptoms domain score was determined based on daily scores of the 6 items. The mean individual symptom item score was determined for each of 6 items and domain score was calculated by summing the mean individual symptom item scores, dividing by number of items, ranged from 0=no cardiopulmonary symptoms, 4=severe cardiopulmonary symptoms. Higher score indicated severe symptoms. FAS: all randomised subjects assigned to a study intervention and analysed according to the intervention received via IWRS. Per change in planned analysis, data for this endpoint was not collected and analysed due to study termination.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to Week 28

End point values	Double Blind (DB) Period: Macitentan	DB Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	0[2]		
Units: Score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[1] - The study was terminated for futility, no subjects were analysed for this endpoint.

[2] - The study was terminated for futility, no subjects were analysed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 28 in PAH-SYMPACT - Cardiovascular Symptom Domain Score

End point title	Change from Baseline to Week 28 in PAH-SYMPACT - Cardiovascular Symptom Domain Score

End point description:

The cardiovascular symptoms domain consisted 5 items: fluttering, rapid heartbeat, chest pain, chest tightness, and lightheadedness, on a scale from 0 (no symptoms at all) to 4 (very severe symptoms). The symptoms part of PAH-SYMPACT was administered daily over 7-day period. The recall period of symptom items was the last 24 hours. An average cardiovascular symptoms domain score was determined based on daily scores of the 5 items. Mean individual symptom item score was determined for each of the 5 items and a domain score was calculated by summing the mean individual symptom item scores and dividing by the number of items, ranged from 0=no cardiovascular symptoms to 4=severe cardiovascular symptoms. Higher score indicated more severe symptoms. FAS: all randomised subjects assigned to a study intervention and were analysed according to the intervention received via IWRS. Per change in planned analysis, data for this endpoint was not collected and analysed due to study termination.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to Week 28

End point values	Double Blind (DB) Period: Macitentan	DB Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: Score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[3] - The study was terminated for futility, no subjects were analysed for this endpoint

[4] - The study was terminated for futility, no subjects were analysed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 28 in Euro Quality of life-5-Dimension-5-Level (EQ-5D-5L) Utility Score

End point title	Change from Baseline to Week 28 in Euro Quality of life-5-Dimension-5-Level (EQ-5D-5L) Utility Score

End point description:

The EQ-5D-5L was a generic measure of health status, a 5-item questionnaire that assessed 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analog scale (VAS). Each questionnaire had 5 response levels: 1 =no problems, 2 =slight problems, 3 =moderate problems, 4 =severe problems and 5 =extreme problems. The scores for the 5 questionnaires were used to compute a single utility score ranged from 0 to 1 representing the general health status of the individual. Higher score indicated better health status. FAS included all randomised subjects assigned to a study intervention and were analysed according to the intervention they had been assigned to via IWRS. Per change in planned analysis, data for this endpoint was not collected and analysed due to study termination.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to Week 28

End point values	Double Blind (DB) Period: Macitentan	DB Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[5] - The study was terminated for futility, no subjects were analysed for this endpoint.

[6] - The study was terminated for futility, no subjects were analysed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 28 in Accelerometer-assessed Proportion

of Time Spent in Moderate to Vigorous Physical Activity

End point title	Change From Baseline to Week 28 in Accelerometer-assessed Proportion of Time Spent in Moderate to Vigorous Physical Activity

End point description:

Change from baseline to week 28 in accelerometer-assessed proportion of time spent in moderate to vigorous physical activity were assessed. The daily life physical activity of the subject was assessed using an accelerometer which was provided to the subject at screening and was worn daily during walking hours up to Week 28. For each scheduled visit, the 14 days prior to the visit was considered as the assessment period for physical activity. A complete day was defined as a record of at least 7 waking hours of data. During these periods, the time spent in different level of activity: sedentary/light/moderate/vigorous was determined based on activity counts per minutes and expressed as proportion relative to the period duration. FAS: all randomised subjects assigned to a study intervention and were analysed according to the intervention they had been assigned to via IWRS. Per change in planned analysis, data for this endpoint was not collected and analysed due to study termination.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to Week 28

End point values	Double Blind (DB) Period: Macitentan	DB Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: Days				
arithmetic mean (standard deviation)	()	()		

Notes:

[7] - The study was terminated for futility, no subjects were analysed for this endpoint.

[8] - The study was terminated for futility, no subjects were analysed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

DB period:DB Day 1 to 30 days post EODBT (median exposure[ME]:24.5 weeks[wks], [min 3.9 wks; max 160.4 wks] on macitentan, ME:44 wks [min 4 wks; max 147.9 wks] on placebo); OL period: OL Day 1 to study termination (ME:72 wks [min 8.1 wks; max 84.6 wks]).

Adverse event reporting additional description:

Safety analysis was based on safety analysis set which included all participants who received at least one dose of study intervention in this study and were analysed according to the intervention they actually received.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Double Blind (DB) Period: Macitentan

Reporting group description:

During the 8-week up-titration phase, subjects received macitentan doses orally once daily (QD): 10 mg tablet for 4 weeks followed by 37.5 mg tablet for another 4 weeks prior to reaching the target maintenance phase dose of macitentan 75 mg QD. Subjects were to remain on double-blind maintenance treatment until the last subject randomised completed the Week 28 visit. Subjects who prematurely discontinued DB study treatment prior to Week 28 but did not withdraw consent were asked to enter post-treatment observation period (PTOP) from DB period last dose until Week 28. Median exposure to DB treatment was 24.50 weeks (minimum: 3.9 weeks; maximum: 160.4 weeks).

Reporting group title	OL Period: DB Placebo

Reporting group description:

Subjects who were treated with placebo in the DB period and had completed the DB period as per protocol were considered eligible to transition into the 104-week OL period and were up-titrated to the target dose of macitentan 75 mg (macitentan 10 mg for 4 weeks, followed by macitentan 37.5 mg for another 4 weeks). Subjects who experienced a clinical worsening event confirmed by the CEC, were allowed to transition to the OL period at any time after Week 28. Median exposure to OL treatment was 72 weeks (minimum: 8.1 weeks; maximum: 84.6 weeks).

Reporting group title	Open Label (OL) Period: DB Macitentan

Reporting group description:

Subjects who were treated with macitentan in the DB period and had reached the target dose of macitentan 75 mg and completed the DB period as per protocol were considered eligible to transition into the 104-week OL period and they continued macitentan 75 mg tablet orally QD from EODBT until study termination. Subjects who experienced a clinical worsening event confirmed by the CEC, were allowed to transition to the OL period at any time after Week 28. Median exposure to OL treatment was 72 weeks (minimum: 8.1 weeks; maximum: 84.6 weeks).

Reporting group title	DB Period: Placebo

Reporting group description:

Subjects received placebo matched to macitentan dose levels during the DB treatment period. Subjects who prematurely discontinued DB study treatment prior to Week 28 but did not withdraw consent were asked to enter PTOP from DB period last dose until Week 28. Median exposure to DB treatment was 44 weeks (minimum: 4 weeks; maximum: 147.9 weeks).

Serious adverse events	Double Blind (DB) Period: Macitentan	OL Period: DB Placebo	Open Label (OL) Period: DB Macitentan
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 64 (26.56%)	4 / 6 (66.67%)	0 / 1 (0.00%)
number of deaths (all causes)	1	0	0

number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast Cancer			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Cancer Metastatic			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep Vein Thrombosis			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post Thrombotic Syndrome			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Ovarian Cystectomy			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Oedema Peripheral			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Abnormal Uterine Bleeding			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural Effusion			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Organising Pneumonia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 6 (16.67%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Failure			

subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Hypertension			
subjects affected / exposed	0 / 64 (0.00%)	2 / 6 (33.33%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal Polyps			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Postoperative Hypertension			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Compression Fracture			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Atrial Tachycardia			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis Coronary Artery			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right Ventricular Failure			
subjects affected / exposed	1 / 64 (1.56%)	1 / 6 (16.67%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus Node Dysfunction			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hemiparesis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient Ischaemic Attack			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo Positional			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			

subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dental Caries			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum Intestinal Haemorrhagic			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large Intestine Polyp			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urge Incontinence			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Lumbar Spinal Stenosis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intervertebral Disc Protrusion			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Respiratory Tract Infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Fluid Retention			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	DB Period: Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 63 (22.22%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast Cancer			

subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal Cancer Metastatic			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neoplasm			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Deep Vein Thrombosis			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post Thrombotic Syndrome			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Ovarian Cystectomy			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Oedema Peripheral			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Reproductive system and breast disorders			
Abnormal Uterine Bleeding			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural Effusion			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Organising Pneumonia			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory Failure			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary Hypertension			

subjects affected / exposed	4 / 63 (6.35%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 0			
Haemothorax				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nasal Polyps				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine Aminotransferase Increased				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aspartate Aminotransferase Increased				
subjects affected / exposed	0 / 63 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Postoperative Hypertension				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal Compression Fracture				
subjects affected / exposed	1 / 63 (1.59%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial Tachycardia				

subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arteriosclerosis Coronary Artery			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Right Ventricular Failure			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinus Node Dysfunction			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Hemiparesis			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient Ischaemic Attack			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo Positional			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Dental Caries			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulum Intestinal Haemorrhagic			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large Intestine Polyp			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urge Incontinence			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Lumbar Spinal Stenosis			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral Disc Protrusion			

subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Respiratory Tract Infection			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Fluid Retention			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Double Blind (DB) Period: Macitentan	OL Period: DB Placebo	Open Label (OL) Period: DB Macitentan
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 64 (73.44%)	5 / 6 (83.33%)	1 / 1 (100.00%)
Investigations			
Haemoglobin Decreased			

subjects affected / exposed	7 / 64 (10.94%)	1 / 6 (16.67%)	0 / 1 (0.00%)
occurrences (all)	7	1	0
Injury, poisoning and procedural complications			
Ligament Sprain			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	1 / 1 (100.00%)
occurrences (all)	1	0	1
Vascular disorders			
Hypotension			
subjects affected / exposed	9 / 64 (14.06%)	1 / 6 (16.67%)	0 / 1 (0.00%)
occurrences (all)	9	1	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 64 (3.13%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	3	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 64 (14.06%)	1 / 6 (16.67%)	0 / 1 (0.00%)
occurrences (all)	13	1	0
Dizziness			
subjects affected / exposed	5 / 64 (7.81%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	6	0	0
Memory Impairment			
subjects affected / exposed	0 / 64 (0.00%)	1 / 6 (16.67%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Oedema Peripheral			
subjects affected / exposed	18 / 64 (28.13%)	1 / 6 (16.67%)	0 / 1 (0.00%)
occurrences (all)	30	1	0
Pyrexia			
subjects affected / exposed	4 / 64 (6.25%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	4	0	0
Swelling			
subjects affected / exposed	0 / 64 (0.00%)	1 / 6 (16.67%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Fatigue			

subjects affected / exposed	4 / 64 (6.25%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	4	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 64 (7.81%)	1 / 6 (16.67%)	0 / 1 (0.00%)
occurrences (all)	6	1	0
Iron Deficiency Anaemia			
subjects affected / exposed	6 / 64 (9.38%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	9	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 64 (1.56%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	2	0	0
Stomatitis			
subjects affected / exposed	1 / 64 (1.56%)	1 / 6 (16.67%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 64 (7.81%)	1 / 6 (16.67%)	0 / 1 (0.00%)
occurrences (all)	6	1	0
Dyspnoea			
subjects affected / exposed	7 / 64 (10.94%)	1 / 6 (16.67%)	0 / 1 (0.00%)
occurrences (all)	7	2	0
Nasal Congestion			
subjects affected / exposed	8 / 64 (12.50%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	10	0	0
Epistaxis			
subjects affected / exposed	1 / 64 (1.56%)	1 / 6 (16.67%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 64 (4.69%)	1 / 6 (16.67%)	0 / 1 (0.00%)
occurrences (all)	3	1	0
Infections and infestations			
Bronchitis			

subjects affected / exposed	3 / 64 (4.69%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	6	0	0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 64 (0.00%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	3 / 64 (4.69%)	1 / 6 (16.67%)	0 / 1 (0.00%)
occurrences (all)	5	1	0
Covid-19			
subjects affected / exposed	15 / 64 (23.44%)	1 / 6 (16.67%)	0 / 1 (0.00%)
occurrences (all)	17	1	0
Metabolism and nutrition disorders			
Iron Deficiency			
subjects affected / exposed	2 / 64 (3.13%)	1 / 6 (16.67%)	0 / 1 (0.00%)
occurrences (all)	2	1	0
Fluid retention			
subjects affected / exposed	4 / 64 (6.25%)	0 / 6 (0.00%)	0 / 1 (0.00%)
occurrences (all)	4	0	0

Non-serious adverse events	DB Period: Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 63 (60.32%)		
Investigations			
Haemoglobin Decreased			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Ligament Sprain			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	2		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			

subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 63 (15.87%)		
occurrences (all)	11		
Dizziness			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	3		
Memory Impairment			
subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
General disorders and administration site conditions			
Oedema Peripheral			
subjects affected / exposed	5 / 63 (7.94%)		
occurrences (all)	5		
Pyrexia			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	4		
Swelling			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	3 / 63 (4.76%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	2		
Iron Deficiency Anaemia			
subjects affected / exposed	2 / 63 (3.17%)		
occurrences (all)	2		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 63 (6.35%)		
occurrences (all)	4		

Stomatitis subjects affected / exposed occurrences (all)	0 / 63 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Nasal Congestion subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	 6 / 63 (9.52%) 9 5 / 63 (7.94%) 5 1 / 63 (1.59%) 1 2 / 63 (3.17%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	 3 / 63 (4.76%) 3		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Covid-19 subjects affected / exposed occurrences (all)	 4 / 63 (6.35%) 4 4 / 63 (6.35%) 9 8 / 63 (12.70%) 8 14 / 63 (22.22%) 14		
Metabolism and nutrition disorders Iron Deficiency			

subjects affected / exposed	1 / 63 (1.59%)		
occurrences (all)	1		
Fluid retention			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 April 2020	The purpose of this amendment was to ensure that all subjects, for whom standard of care with riociguat was appropriate, received riociguat in the study. Furthermore, information on the ongoing drug-drug interaction (DDI) study with riociguat was provided, and the criteria for concomitant riociguat therapy (in the absence of a clinically relevant DDI) to be permitted without the need for a substantial amendment were defined.
13 July 2020	The purpose of this amendment was to update the exclusion criteria and concomitant therapy sections pertaining to new information regarding a DDI of macitentan 75 mg with moderate dual Cytochrome (CYP)3A4 and CYP2C9 inhibitors or co-administration of a combination of moderate CYP3A4 inhibitors and moderate CYP2C9 inhibitors.
05 August 2020	The purpose of this amendment was to 1. include the changes related to the use of riociguat and the DDI study that were mandated by voluntary harmonisation procedure (VHP), 2. to implement changes due to an urgent safety measure (USM) (that is, exclusion of subjects treated with dual moderate CYP3A4/CYP2C9 inhibitors), 3. to allow the use of subcutaneous (SC) treprostinil as background pulmonary hypertension (PH)-specific therapy, since it had received marketing authorisation in the European Union (EU) in April 2020, 4. to update the statistical section based on European Medicines Agency (EMA) Scientific Advice as well as to make minor updates and corrections and perform editorial document formatting revisions.
15 December 2020	The purpose of this amendment was to modify the study design for increasing the double-blind (DB) follow-up time. This increase in the DB follow-up time improved the statistical power for the key secondary endpoint (time to clinical worsening). Also, a new substudy was added to provide additional safety data of chronic treatment with macitentan on testicular function in patients with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH). Specific requirements for Japanese sites were added. Minor corrections and editorial revisions were also being implemented.

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.

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

Notes: