Clinical trial results:
The Efficacy and Safety of Initial Triple Versus Initial Dual Oral combination therapy in patients with newly diagnosed Pulmonary Arterial Hypertension: A Multicenter, Double-Blind, Placebo-controlled, Phase 3b study.

Summary

EudraCT number	2015-003438-28
Trial protocol	DE NO FR DK AT GB ES BE
Global end of trial date	05 May 2020

Results information

Result version number	v1 (current)
This version publication date	08 April 2021
First version publication date	08 April 2021

Trial information

Trial identification

Sponsor protocol code	AC-065A308

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02558231
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	05 May 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to compare the effect on pulmonary vascular resistance (PVR) of an initial triple oral regimen (macitentan, tadalafil, selexipag) versus an initial dual oral regimen (macitentan, tadalafil, placebo) in newly diagnosed, treatment-naïve subjects with pulmonary arterial hypertension (PAH).

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Safety was evaluated based on the following assessments: adverse events (AEs), serious adverse events (SAEs), deaths, clinical laboratory tests (hematology, clinical chemistry, pregnancy tests), vital signs, body weight, and physical examination.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 April 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Austria: 14
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Canada: 25
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Germany: 36
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	United States: 114

Worldwide total number of subjects	247
EEA total number of subjects	97

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)	194
From 65 to 84 years	53
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 247 subjects (123 subjects in Triple therapy and 124 subjects in Double therapy) were enrolled in the study. Out of the 247 subjects, 196 subjects completed the study (98 subjects in each arm).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag)

Arm description:

Subjects received macitentan oral tablet, 10 milligrams (mg) once daily and tadalafil oral tablet, 20 mg, once daily from Day 1 up to End of treatment (10 months after last subjects was enrolled). Tadalafil was up-titrated from 20 mg to 40 mg on Day 8. In addition, subjects received selexipag oral tablet at a starting dose of 200 micrograms (mcg), twice daily from Day 15 up-titrated to a maximum of 1600 mcg, up to End of treatment (10 months after last subjects was enrolled).

Arm type	Experimental
Investigational medicinal product name	Macitentan 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Macitentan 10 mg tablet administered once daily on Day 1.

Investigational medicinal product name	Selexipag 200 micrograms (mcg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Selexipag 200 mcg tablet administered twice daily (bid) on Day 15 and dose uptitrated in increments of 200 mcg bid, at weekly intervals until either a maximum dose of 1600 mcg bid was reached or adverse pharmacological effects that could not be tolerated or medically managed were experienced, whichever was first.

Investigational medicinal product name	Tadalafil 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tadalafil 20 mg tablet administered once daily on Day 1 and dose increased to 40 mg (2 tablets) once daily on Day 8.

Arm title	Double Oral Therapy (Macitentan, Tadalafil, and Placebo)

Arm description:

Subjects received macitentan oral tablet, 10 mg once daily and tadalafil oral tablet, 20 once daily from Day 1 up to End of treatment (10 months after last subjects was enrolled). Tadalafil was up-titrated from 20 mg to 40 mg on Day 8. In addition, subjects received placebo matching to selexipag oral tablet, at a starting dose of 200 micrograms (mcg), twice daily from Day 15 and dose up-titrated to a maximum of 1600 mcg, up to End of treatment (10 months after last subjects was enrolled).

Arm type	Placebo
Investigational medicinal product name	Macitentan 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Macitentan 10 mg tablet administered once daily on Day 1.

Investigational medicinal product name	Tadalafil 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tadalafil 20 mg tablet administered once daily on Day 1 and dose increased to 40 mg (2 tablets) once daily on Day 8.

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

Dosage and administration details:

Matching placebo tablet administered twice daily (bid) from Day 15 to End of treatment (10 months after last subject enrolled).

Number of subjects in period 1	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag)	Double Oral Therapy (Macitentan, Tadalafil, and Placebo)
Started	123	124
Treated	123	123
Completed	98	98
Not completed	25	26
Adverse event, serious fatal	4	12
Physician decision	7	5
Consent withdrawn by subject	7	4
Lost to follow-up	7	4
Sponsor decision	-	1

Baseline characteristics

Reporting groups

Reporting group title	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag)

Reporting group description:

Subjects received macitentan oral tablet, 10 milligrams (mg) once daily and tadalafil oral tablet, 20 mg, once daily from Day 1 up to End of treatment (10 months after last subjects was enrolled). Tadalafil was up-titrated from 20 mg to 40 mg on Day 8. In addition, subjects received selexipag oral tablet at a starting dose of 200 micrograms (mcg), twice daily from Day 15 up-titrated to a maximum of 1600 mcg, up to End of treatment (10 months after last subjects was enrolled).

Reporting group title	Double Oral Therapy (Macitentan, Tadalafil, and Placebo)

Reporting group description:

Subjects received macitentan oral tablet, 10 mg once daily and tadalafil oral tablet, 20 once daily from Day 1 up to End of treatment (10 months after last subjects was enrolled). Tadalafil was up-titrated from 20 mg to 40 mg on Day 8. In addition, subjects received placebo matching to selexipag oral tablet, at a starting dose of 200 micrograms (mcg), twice daily from Day 15 and dose up-titrated to a maximum of 1600 mcg, up to End of treatment (10 months after last subjects was enrolled).

Reporting group values	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag)	Double Oral Therapy (Macitentan, Tadalafil, and Placebo)	Total
Number of subjects	123	124	247
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	96	98	194
From 65 to 84 years	27	26	53
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	52.2	51.6	
standard deviation	± 13.48	± 13.92	-
Title for Gender Units: subjects			
Female	93	94	187
Male	30	30	60

End points

End points reporting groups

Reporting group title	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag)
Reporting group description:	
Subjects received macitentan oral tablet, 10 milligrams (mg) once daily and tadalafil oral tablet, 20 mg, once daily from Day 1 up to End of treatment (10 months after last subjects was enrolled). Tadalafil was up-titrated from 20 mg to 40 mg on Day 8. In addition, subjects received selexipag oral tablet at a starting dose of 200 micrograms (mcg), twice daily from Day 15 up-titrated to a maximum of 1600 mcg, up to End of treatment (10 months after last subjects was enrolled).	
Reporting group title	Double Oral Therapy (Macitentan, Tadalafil, and Placebo)
Reporting group description:	
Subjects received macitentan oral tablet, 10 mg once daily and tadalafil oral tablet, 20 once daily from Day 1 up to End of treatment (10 months after last subjects was enrolled). Tadalafil was up-titrated from 20 mg to 40 mg on Day 8. In addition, subjects received placebo matching to selexipag oral tablet, at a starting dose of 200 micrograms (mcg), twice daily from Day 15 and dose up-titrated to a maximum of 1600 mcg, up to End of treatment (10 months after last subjects was enrolled).	

Primary: Change from Baseline to Week 26 in Pulmonary Vascular Resistance (PVR)

End point title	Change from Baseline to Week 26 in Pulmonary Vascular Resistance (PVR)
End point description:	
Change from baseline to Week 26 in PVR was expressed as the ratio of Week 26 to baseline PVR value (Week 26 divided by baseline) using re-calculated PVR. PVR was determined by right heart catheterization (RHC). A geometric least square mean ratio of Week 26 to baseline PVR less than (<) 1 corresponds to a reduction in PVR from baseline. Missing values were imputed using a last observation carried forward (LOCF) approach. Full analysis set (FAS) included all randomized subjects.	
End point type	Primary
End point timeframe:	
Baseline, Week 26	

End point values	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag)	Double Oral Therapy (Macitentan, Tadalafil, and Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	124		
Units: ratio				
least squares mean (confidence interval 95%)	0.46 (0.422 to 0.503)	0.48 (0.441 to 0.526)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Subjects analyzed were 123 and 124 in Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag) and Double Oral Therapy (Macitentan, Tadalafil, and Placebo) arms, respectively.	
Comparison groups	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag) v

	Double Oral Therapy (Macitentan, Tadalafil, and Placebo)
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4239
Method	ANCOVA
Parameter estimate	Ratio of geometric Least Square mean
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.856
upper limit	1.068

Secondary: Change from Baseline to Week 26 in 6-minute Walk Distance (6MWD)

End point title	Change from Baseline to Week 26 in 6-minute Walk Distance (6MWD)

End point description:

The change from baseline to Week 26 in 6MWD was calculated as Week 26 minus baseline. The test measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface. The goal is for the individual to walk as far as possible in six minutes. Missing values were imputed using a LOCF approach. FAS included all randomized subjects. Here, N (number of subjects analyzed) signifies the number of subjects analyzed for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag)	Double Oral Therapy (Macitentan, Tadalafil, and Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	121		
Units: meter				
least squares mean (confidence interval 95%)	54.96 (40.419 to 69.501)	56.39 (41.447 to 71.327)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Subjects analyzed were 123 and 121 in Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag) and Double Oral Therapy (Macitentan, Tadalafil, and Placebo) arms, respectively.

Comparison groups	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag) v Double Oral Therapy (Macitentan, Tadalafil, and Placebo)

Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8758
Method	ANCOVA
Parameter estimate	Least Square (LS) Mean difference
Point estimate	-1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.393
upper limit	16.538

Secondary: Change from Baseline to Week 26 in N-terminal pro B-type Natriuretic Peptide (NT-proBNP) Levels

End point title	Change from Baseline to Week 26 in N-terminal pro B-type Natriuretic Peptide (NT-proBNP) Levels

End point description:

The change from baseline to Week 26 in NT-proBNP was expressed as the ratio of Week 26 to baseline NT-proBNP (Week 26 divided by baseline). A geometric least square mean ratio of Week 26 to baseline NT-proBNP <1 corresponds to a reduction in NT-proBNP from baseline. Missing values were imputed using a LOCF approach. FAS included all randomized subjects. Here, N (number of subjects analyzed) signifies the number of subjects analyzed for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag)	Double Oral Therapy (Macitentan, Tadalafil, and Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	122		
Units: ratio				
least squares mean (confidence interval 95%)	0.26 (0.206 to 0.328)	0.25 (0.200 to 0.320)		

Statistical analyses

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Subjects analyzed were 121 and 122 in Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag) and Double Oral Therapy (Macitentan, Tadalafil, and Placebo) arms, respectively.

Comparison groups	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag) v Double Oral Therapy (Macitentan, Tadalafil, and Placebo)

Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8529
Method	ANCOVA
Parameter estimate	Ratio of LS mean
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.371

Secondary: Percentage of Subjects with Absence of Worsening from Baseline to Week 26 in World Health Organization (WHO) Functional Class (FC)

End point title	Percentage of Subjects with Absence of Worsening from Baseline to Week 26 in World Health Organization (WHO) Functional Class (FC)

End point description:

WHO FC is a classification graded from Class I to IV which reflects disease severity based on symptoms. Worsening was defined as death or hospitalization due to PAH. Class I: No limitation of activity; Class II: slight limitation with ordinary activities; Class III: may not have symptoms at rest but greatly limited activities; Class IV: symptoms at rest and inability to carry out any physical activity without symptoms. Missing values were imputed using a LOCF approach. FAS included all randomized subjects. Here, N (number of subjects analyzed) signifies number of subjects analyzed for this endpoint. Subjects with WHO FC IV at baseline were excluded from this analysis as they could not shift to a worse category.

End point type	Secondary

End point timeframe:

Week 26

End point values	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag)	Double Oral Therapy (Macitentan, Tadalafil, and Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	119		
Units: Number				
number (not applicable)	99.2	97.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 26 in Mean Pulmonary Arterial Pressure (mPAP)

End point title	Change from Baseline to Week 26 in Mean Pulmonary Arterial Pressure (mPAP)

End point description:

Change from baseline to Week 26 in mean Pulmonary Arterial Pressure (mPAP) was measured. The pulmonary artery pressure is a measure of the blood pressure found in the main pulmonary artery. Missing values were imputed using a LOCF approach. FAS included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag)	Double Oral Therapy (Macitentan, Tadalafil, and Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	124		
Units: millimeters of mercury (mmHg)				
least squares mean (confidence interval 95%)	-12.92 (-14.609 to -11.235)	-12.20 (-13.881 to -10.515)		

Statistical analyses

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Subjects analyzed were 123 and 124 in Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag) and Double Oral Therapy (Macitentan, Tadalafil, and Placebo) arms, respectively.

Comparison groups	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag) v Double Oral Therapy (Macitentan, Tadalafil, and Placebo)
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4998
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.834
upper limit	1.386

Secondary: Change from Baseline to Week 26 in Mean Right Atrial Pressure (mRAP)

End point title	Change from Baseline to Week 26 in Mean Right Atrial Pressure (mRAP)

End point description:

Change from baseline to Week 26 in mean Right Atrial Pressure (mRAP) was measured. Missing values were imputed using a LOCF approach. FAS included all randomized subjects. Here, N (number of subjects analyzed) signifies the number of subjects analyzed for this endpoint.

End point type	Secondary
End point timeframe:	
Baseline, Week 26	

End point values	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag)	Double Oral Therapy (Macitentan, Tadalafil, and Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	123		
Units: mmHg				
least squares mean (confidence interval 95%)	-1.78 (-2.512 to -1.045)	-1.69 (-2.429 to -0.955)		

Statistical analyses

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Subjects analyzed were 123 each in both Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag) and Double Oral Therapy (Macitentan, Tadalafil, and Placebo) arms.	
Comparison groups	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag) v Double Oral Therapy (Macitentan, Tadalafil, and Placebo)
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8528
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.003
upper limit	0.83

Secondary: Change from Baseline to Week 26 in Total Pulmonary Resistance

End point title	Change from Baseline to Week 26 in Total Pulmonary Resistance
End point description:	
Change from baseline to Week 26 in total pulmonary resistance was measured. Total pulmonary resistance was calculated as mPAP/CO*80, where CO is cardiac output. Re-calculated values were used for analysis and missing values were imputed using a LOCF approach. FAS included all randomized subjects.	
End point type	Secondary
End point timeframe:	
Baseline, Week 26	

End point values	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag)	Double Oral Therapy (Macitentan, Tadalafil, and Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	124		
Units: dynes*second per centimeter^5				
least squares mean (confidence interval 95%)	-511.88 (-569.36 to -454.40)	-514.28 (-571.45 to -457.11)		

Statistical analyses

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
Subjects analyzed were 123 and 124 in Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag) and Double Oral Therapy (Macitentan, Tadalafil, and Placebo) arms, respectively.	
Comparison groups	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag) v Double Oral Therapy (Macitentan, Tadalafil, and Placebo)
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9474
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-69.368
upper limit	74.178

Secondary: Change from Baseline to Week 26 in Cardiac Index

End point title	Change from Baseline to Week 26 in Cardiac Index
End point description:	
Change from baseline to Week 26 in cardiac index was measured. Cardiac index is the amount of blood pumped by the heart, per minute, per meter square of body surface area. Re-calculated values were used for analysis and missing values were imputed using a LOCF approach. FAS included all randomized subjects.	
End point type	Secondary
End point timeframe:	
Baseline, Week 26	

End point values	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag)	Double Oral Therapy (Macitentan, Tadalafil, and Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	124		
Units: liters per minute per meter square				
least squares mean (confidence interval 95%)	0.97 (0.814 to 1.130)	0.84 (0.684 to 0.997)		

Statistical analyses

Statistical analysis title	Statistical Analysis 7
Statistical analysis description:	
Subjects analyzed were 123 and 124 in Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag) and Double Oral Therapy (Macitentan, Tadalafil, and Placebo) arms, respectively.	
Comparison groups	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag) v Double Oral Therapy (Macitentan, Tadalafil, and Placebo)
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1902
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.066
upper limit	0.328

Secondary: Change from Baseline to Week 26 in Venous Oxygen Saturation (%)

End point title	Change from Baseline to Week 26 in Venous Oxygen Saturation (%)
End point description:	
Change from baseline to Week 26 in venous oxygen saturation was measured. Missing values were imputed using a LOCF approach. FAS included all randomized subjects. Here, N (number of subjects analyzed) signifies the number of subjects analyzed for this endpoint.	
End point type	Secondary
End point timeframe:	
Baseline, Week 26	

End point values	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag)	Double Oral Therapy (Macitentan, Tadalafil, and Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	118		
Units: percentage of oxygen saturation				
least squares mean (confidence interval 95%)	5.59 (4.370 to 6.801)	6.79 (5.561 to 8.020)		

Statistical analyses

Statistical analysis title	Statistical Analysis 8

Statistical analysis description:

Subjects analyzed were 120 and 118 in Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag) and Double Oral Therapy (Macitentan, Tadalafil, and Placebo) arms, respectively.

Comparison groups	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag) v Double Oral Therapy (Macitentan, Tadalafil, and Placebo)
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1227
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.737
upper limit	0.327

Secondary: Number of Subjects with Disease Progression Event

End point title	Number of Subjects with Disease Progression Event

End point description:

Number of subjects with disease progression event were reported. Disease progression event as adjudicated by the CEC, defined as any of the following: a. Death (all causes; adjudicated for PAH relationship); b. Hospitalization for worsening PAH; c. Initiation of prostacyclin, a prostacyclin analog, or a prostacyclin receptor agonist for worsening PAH; d. Clinical worsening defined as a post-baseline decrease in 6MWD by more than (>) 15 percent (%) from the highest 6MWD obtained at or after baseline, accompanied by WHO FC III or IV (both conditions confirmed at two consecutive post-baseline visits separated by 1–21 days). FAS included all randomized subjects.

End point type	Secondary

End point timeframe:

Week 26, Month 12, Month 18, Month 24, Month 30, and End of Analysis Period (up to 40 months)

End point values	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag)	Double Oral Therapy (Macitentan, Tadalafil, and Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	124		
Units: subjects				
number (not applicable)				
Week 26	8	13		
Month 12	13	20		
Month 18	15	23		
Month 24	15	25		
Month 30	16	27		
End of Analysis Period (up to 40 months)	16	27		

Statistical analyses

Statistical analysis title	Statistical Analysis 9
Statistical analysis description:	
Subjects analyzed were 123 and 124 in Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag) and Double Oral Therapy (Macitentan, Tadalafil, and Placebo) arms, respectively.	
Comparison groups	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag) v Double Oral Therapy (Macitentan, Tadalafil, and Placebo)
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0867
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	1.09

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 42 Months

Adverse event reporting additional description:

The Safety Set included all subjects who received at least one dose of any of 3 study treatments (macitentan, tadalafil, and selexipag or placebo) (Triple oral therapy=123 subjects and Double oral therapy=123 subjects). Four subjects in triple therapy group did not receive selexipag and were analyzed in the double therapy group for safety analysis.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Double Oral Therapy (Macitentan, Tadalafil, and Placebo)

Reporting group description:

Subjects received macitentan oral tablet, 10 mg once daily and tadalafil oral tablet, 20 once daily from Day 1 up to End of treatment (10 months after last subjects was enrolled). Tadalafil was up-titrated from 20 mg to 40 mg on Day 8. In addition, subjects received placebo matching to selexipag oral tablet, at a starting dose of 200 micrograms (mcg), twice daily from Day 15 and dose up-titrated to a maximum of 1600 mcg, up to End of treatment (10 months after last subjects was enrolled).

Reporting group title	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag)

Reporting group description:

Subjects received macitentan oral tablet, 10 milligrams (mg) once daily and tadalafil oral tablet, 20 mg, once daily from Day 1 up to End of treatment (10 months after last subjects was enrolled). Tadalafil was up-titrated from 20 mg to 40 mg on Day 8. In addition, subjects received selexipag oral tablet at a starting dose of 200 micrograms (mcg), twice daily from Day 15 up-titrated to a maximum of 1600 mcg, up to End of treatment (10 months after last subjects was enrolled).

Serious adverse events	Double Oral Therapy (Macitentan, Tadalafil, and Placebo)	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag)	
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 127 (37.80%)	58 / 119 (48.74%)	
number of deaths (all causes)	12	4	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast Cancer			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive Ductal Breast Carcinoma			

subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Carcinoma Cell Type Unspecified Stage I			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Neoplasm Malignant			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant Melanoma			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma Cell Myeloma			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma of the Tongue			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	2 / 127 (1.57%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive Crisis			

subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 127 (1.57%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paradoxical Embolism			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock Haemorrhagic			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Drug Delivery Device Implantation			
subjects affected / exposed	1 / 127 (0.79%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip Arthroplasty			
subjects affected / exposed	2 / 127 (1.57%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Knee Arthroplasty			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Transplant			

subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Open Reduction of Fracture			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Penile Operation			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial Drainage			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Therapy Change			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toe Amputation			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Accidental Death			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-Cardiac Chest Pain			
subjects affected / exposed	3 / 127 (2.36%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema Peripheral			

subjects affected / exposed	1 / 127 (0.79%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden Cardiac Death			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden Death			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Allergy to Arthropod Sting			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Priapism			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			

subjects affected / exposed	5 / 127 (3.94%)	6 / 119 (5.04%)	
occurrences causally related to treatment / all	0 / 8	2 / 8	
deaths causally related to treatment / all	0 / 1	0 / 0	
Choking			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 127 (0.00%)	5 / 119 (4.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Epistaxis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 127 (1.57%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Interstitial Lung Disease			
subjects affected / exposed	0 / 127 (0.00%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	1 / 127 (0.79%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			

subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Aspiration			
subjects affected / exposed	2 / 127 (1.57%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary Arterial Hypertension			
subjects affected / exposed	8 / 127 (6.30%)	8 / 119 (6.72%)	
occurrences causally related to treatment / all	0 / 10	0 / 10	
deaths causally related to treatment / all	0 / 1	0 / 2	
Pulmonary Embolism			
subjects affected / exposed	1 / 127 (0.79%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary Hypertension			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Mass			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Oedema			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Veno-Occlusive Disease			
subjects affected / exposed	3 / 127 (2.36%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory Arrest			

subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory Distress			
subjects affected / exposed	2 / 127 (1.57%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			
subjects affected / exposed	1 / 127 (0.79%)	6 / 119 (5.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 8	
deaths causally related to treatment / all	0 / 1	0 / 1	
Psychiatric disorders			
Confusional State			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic Disorder			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device Dislocation			
subjects affected / exposed	0 / 127 (0.00%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Pressure Increased			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Electrophysiologic Study			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheterisation Cardiac			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin Decreased			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Enzyme Increased			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza A Virus Test Positive			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Function Test Increased			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotavirus Test Positive			

subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep Study			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases Increased			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant Evaluation			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Waist Circumference Increased			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Chest Injury			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep Vein Thrombosis Postoperative			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fall			
subjects affected / exposed	1 / 127 (0.79%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip Fracture			

subjects affected / exposed	1 / 127 (0.79%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional Overdose			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Procedural Haemorrhage			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib Fracture			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road Traffic Accident			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Compression Fracture			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic Vertebral Fracture			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to Various Agents			

subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular Pseudoaneurysm			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist Fracture			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Gastrointestinal Arteriovenous Malformation			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Left Ventricular Failure			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute Right Ventricular Failure			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	2 / 127 (1.57%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial Flutter			
subjects affected / exposed	2 / 127 (1.57%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Tachycardia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	2 / 127 (1.57%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac Failure			
subjects affected / exposed	1 / 127 (0.79%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac Failure Acute			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac Failure Chronic			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	1 / 127 (0.79%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure High Output			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic Shock			

subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Disease			
subjects affected / exposed	2 / 127 (1.57%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Cardiomyopathy			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left Ventricular Failure			
subjects affected / exposed	1 / 127 (0.79%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial Effusion			
subjects affected / exposed	3 / 127 (2.36%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right Ventricular Failure			
subjects affected / exposed	8 / 127 (6.30%)	6 / 119 (5.04%)	
occurrences causally related to treatment / all	0 / 11	1 / 8	
deaths causally related to treatment / all	0 / 3	0 / 1	
Sinus Tachycardia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular Tachycardia			

subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Tachycardia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral Infarction			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic Stroke			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic Stroke			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ischaemic Stroke			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	6 / 127 (4.72%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 127 (1.57%)	3 / 119 (2.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Loss Anaemia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron Deficiency Anaemia			
subjects affected / exposed	1 / 127 (0.79%)	3 / 119 (2.52%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microcytic Anaemia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness Neurosensory			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Blindness			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal Haemorrhage			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Amyloidosis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Haemorrhage			
subjects affected / exposed	2 / 127 (1.57%)	3 / 119 (2.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal Polyp Haemorrhage			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated Umbilical Hernia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Ischaemia			

subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestinal Haemorrhage			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 127 (0.79%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal Haemorrhage			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Prolapse			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal Haemorrhage			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Obstruction			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Gastrointestinal Haemorrhage			

subjects affected / exposed	0 / 127 (0.00%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 127 (1.57%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune Hepatitis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-Induced Liver Injury			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Cirrhosis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Failure			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Disorder			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin Ulcer			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute Kidney Injury			
subjects affected / exposed	1 / 127 (0.79%)	3 / 119 (2.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy Toxic			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal Failure			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Amyloidosis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal Impairment			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scleroderma Renal Crisis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chest Wall Haematoma			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Costochondritis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular Weakness			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 127 (0.00%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic Scleroderma			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 127 (1.57%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Related Infection			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia Sepsis			

subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Viral			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Infection			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 127 (0.79%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis Chronic			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 127 (3.15%)	8 / 119 (6.72%)	
occurrences causally related to treatment / all	0 / 4	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Legionella			

subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Pseudomonal			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Acute			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 127 (2.36%)	4 / 119 (3.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic Shock			
subjects affected / exposed	1 / 127 (0.79%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Bacteraemia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 127 (1.57%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	2 / 127 (1.57%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urosepsis			

subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Device Infection			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 127 (1.57%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to Thrive			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid Overload			
subjects affected / exposed	0 / 127 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 127 (0.79%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 127 (0.79%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Double Oral Therapy (Macitentan, Tadalafil, and Placebo)	Triple Oral Therapy (Macitentan, Tadalafil, and Selexipag)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	119 / 127 (93.70%)	118 / 119 (99.16%)	
Vascular disorders			
Flushing			
subjects affected / exposed	22 / 127 (17.32%)	21 / 119 (17.65%)	
occurrences (all)	25	27	
Hypotension			
subjects affected / exposed	8 / 127 (6.30%)	10 / 119 (8.40%)	
occurrences (all)	9	11	
General disorders and administration site conditions			
Chest Discomfort			
subjects affected / exposed	10 / 127 (7.87%)	7 / 119 (5.88%)	
occurrences (all)	14	8	
Chest Pain			
subjects affected / exposed	4 / 127 (3.15%)	6 / 119 (5.04%)	
occurrences (all)	4	7	
Chills			
subjects affected / exposed	2 / 127 (1.57%)	7 / 119 (5.88%)	
occurrences (all)	2	7	
Fatigue			
subjects affected / exposed	22 / 127 (17.32%)	24 / 119 (20.17%)	
occurrences (all)	26	30	
Influenza Like Illness			
subjects affected / exposed	7 / 127 (5.51%)	6 / 119 (5.04%)	
occurrences (all)	7	6	
Non-Cardiac Chest Pain			
subjects affected / exposed	6 / 127 (4.72%)	10 / 119 (8.40%)	
occurrences (all)	8	11	
Oedema Peripheral			
subjects affected / exposed	46 / 127 (36.22%)	45 / 119 (37.82%)	
occurrences (all)	58	57	
Pain			

subjects affected / exposed	9 / 127 (7.09%)	11 / 119 (9.24%)	
occurrences (all)	10	14	
Peripheral Swelling			
subjects affected / exposed	4 / 127 (3.15%)	11 / 119 (9.24%)	
occurrences (all)	8	11	
Pyrexia			
subjects affected / exposed	11 / 127 (8.66%)	11 / 119 (9.24%)	
occurrences (all)	13	14	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	23 / 127 (18.11%)	19 / 119 (15.97%)	
occurrences (all)	25	23	
Dyspnoea			
subjects affected / exposed	25 / 127 (19.69%)	20 / 119 (16.81%)	
occurrences (all)	36	27	
Epistaxis			
subjects affected / exposed	13 / 127 (10.24%)	13 / 119 (10.92%)	
occurrences (all)	14	14	
Hypoxia			
subjects affected / exposed	7 / 127 (5.51%)	6 / 119 (5.04%)	
occurrences (all)	7	6	
Nasal Congestion			
subjects affected / exposed	23 / 127 (18.11%)	22 / 119 (18.49%)	
occurrences (all)	24	23	
Oropharyngeal Pain			
subjects affected / exposed	2 / 127 (1.57%)	9 / 119 (7.56%)	
occurrences (all)	2	11	
Pulmonary Arterial Hypertension			
subjects affected / exposed	3 / 127 (2.36%)	8 / 119 (6.72%)	
occurrences (all)	3	9	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 127 (3.94%)	9 / 119 (7.56%)	
occurrences (all)	6	9	
Insomnia			

subjects affected / exposed	6 / 127 (4.72%)	8 / 119 (6.72%)	
occurrences (all)	6	8	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	4 / 127 (3.15%)	8 / 119 (6.72%)	
occurrences (all)	4	11	
Aspartate Aminotransferase Increased			
subjects affected / exposed	4 / 127 (3.15%)	10 / 119 (8.40%)	
occurrences (all)	4	13	
Haemoglobin Decreased			
subjects affected / exposed	6 / 127 (4.72%)	10 / 119 (8.40%)	
occurrences (all)	7	12	
Weight Increased			
subjects affected / exposed	8 / 127 (6.30%)	5 / 119 (4.20%)	
occurrences (all)	9	6	
Cardiac disorders			
Palpitations			
subjects affected / exposed	11 / 127 (8.66%)	14 / 119 (11.76%)	
occurrences (all)	11	16	
Nervous system disorders			
Dizziness			
subjects affected / exposed	27 / 127 (21.26%)	17 / 119 (14.29%)	
occurrences (all)	30	18	
Headache			
subjects affected / exposed	78 / 127 (61.42%)	83 / 119 (69.75%)	
occurrences (all)	110	144	
Hypoaesthesia			
subjects affected / exposed	1 / 127 (0.79%)	6 / 119 (5.04%)	
occurrences (all)	1	9	
Paraesthesia			
subjects affected / exposed	2 / 127 (1.57%)	8 / 119 (6.72%)	
occurrences (all)	2	10	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 127 (8.66%)	14 / 119 (11.76%)	
occurrences (all)	12	16	

Iron Deficiency Anaemia			
subjects affected / exposed	5 / 127 (3.94%)	6 / 119 (5.04%)	
occurrences (all)	6	7	
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	4 / 127 (3.15%)	6 / 119 (5.04%)	
occurrences (all)	7	7	
Abdominal Pain			
subjects affected / exposed	6 / 127 (4.72%)	7 / 119 (5.88%)	
occurrences (all)	7	8	
Abdominal Pain Upper			
subjects affected / exposed	7 / 127 (5.51%)	8 / 119 (6.72%)	
occurrences (all)	11	10	
Constipation			
subjects affected / exposed	9 / 127 (7.09%)	7 / 119 (5.88%)	
occurrences (all)	11	8	
Diarrhoea			
subjects affected / exposed	41 / 127 (32.28%)	66 / 119 (55.46%)	
occurrences (all)	60	99	
Dyspepsia			
subjects affected / exposed	17 / 127 (13.39%)	27 / 119 (22.69%)	
occurrences (all)	18	31	
Gastrooesophageal Reflux Disease			
subjects affected / exposed	18 / 127 (14.17%)	11 / 119 (9.24%)	
occurrences (all)	21	12	
Nausea			
subjects affected / exposed	33 / 127 (25.98%)	56 / 119 (47.06%)	
occurrences (all)	40	73	
Vomiting			
subjects affected / exposed	14 / 127 (11.02%)	30 / 119 (25.21%)	
occurrences (all)	15	37	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	9 / 127 (7.09%)	6 / 119 (5.04%)	
occurrences (all)	9	9	
Swelling Face			

subjects affected / exposed	2 / 127 (1.57%)	8 / 119 (6.72%)	
occurrences (all)	2	8	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 127 (14.96%)	19 / 119 (15.97%)	
occurrences (all)	26	25	
Back Pain			
subjects affected / exposed	19 / 127 (14.96%)	13 / 119 (10.92%)	
occurrences (all)	26	14	
Muscle Spasms			
subjects affected / exposed	7 / 127 (5.51%)	9 / 119 (7.56%)	
occurrences (all)	7	11	
Musculoskeletal Pain			
subjects affected / exposed	1 / 127 (0.79%)	8 / 119 (6.72%)	
occurrences (all)	1	9	
Myalgia			
subjects affected / exposed	19 / 127 (14.96%)	21 / 119 (17.65%)	
occurrences (all)	25	30	
Pain in Extremity			
subjects affected / exposed	24 / 127 (18.90%)	37 / 119 (31.09%)	
occurrences (all)	29	46	
Pain in Jaw			
subjects affected / exposed	15 / 127 (11.81%)	35 / 119 (29.41%)	
occurrences (all)	19	36	
Infections and infestations			
Bronchitis			
subjects affected / exposed	6 / 127 (4.72%)	6 / 119 (5.04%)	
occurrences (all)	8	7	
Influenza			
subjects affected / exposed	7 / 127 (5.51%)	6 / 119 (5.04%)	
occurrences (all)	9	6	
Nasopharyngitis			
subjects affected / exposed	23 / 127 (18.11%)	20 / 119 (16.81%)	
occurrences (all)	38	30	
Sinusitis			

subjects affected / exposed	8 / 127 (6.30%)	5 / 119 (4.20%)	
occurrences (all)	10	6	
Upper Respiratory Tract Infection			
subjects affected / exposed	21 / 127 (16.54%)	14 / 119 (11.76%)	
occurrences (all)	30	17	
Urinary Tract Infection			
subjects affected / exposed	11 / 127 (8.66%)	9 / 119 (7.56%)	
occurrences (all)	16	11	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	4 / 127 (3.15%)	14 / 119 (11.76%)	
occurrences (all)	4	14	
Fluid Retention			
subjects affected / exposed	8 / 127 (6.30%)	6 / 119 (5.04%)	
occurrences (all)	11	8	
Hypokalaemia			
subjects affected / exposed	15 / 127 (11.81%)	17 / 119 (14.29%)	
occurrences (all)	18	21	
Iron Deficiency			
subjects affected / exposed	7 / 127 (5.51%)	3 / 119 (2.52%)	
occurrences (all)	8	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2016	This amendment dated 10 Jun 2016 (Protocol Version 2) was considered substantial and included changes based on requests from health authorities or Ethics Committees (ECs)/Institutional Review Boards (IRBs), feedback received from investigators on Protocol Version 1 to improve study feasibility, and an update based on selexipag final prescribing information. The main changes were: exclusion criterion on stroke was modified to include cerebrovascular events (in addition to stroke) and exclusion criterion on interstitial lung disease was clarified to include evidence of the condition based on a computed tomography scan. In addition, local laboratory assessments were allowed for assessing the eligibility of subjects at screening when performed with the central laboratory kit in parallel. Reporting requirement for cardiopulmonary rehabilitation program was added to the allowed and forbidden concomitant therapy lists. For the investigational product (selexipag or placebo), a once-daily regimen was recommended for subjects with moderate hepatic impairment due to increased exposure to selexipag and its active metabolite. Hyper-/hypothyroidism was added to the study-specific criteria on study treatment interruption and/or discontinuation.
09 February 2017	This amendment dated 9 Feb 2017 (Protocol Version 3) was considered substantial and included the following changes: new information on drug-drug interactions was included for selexipag (concomitant therapy lists [allowed and forbidden]); exclusion criteria, and study-specific treatment discontinuation criteria updated for treatment with strong inhibitors of Cytochrome P450 Family 2 Subfamily C Member 8 (CYP2C8) (example, gemfibrozil) and moderate inducers of CYP2C8 (example, rifampicin); new information on risks of selexipag were added.
16 August 2017	This amendment dated 16 Aug 2017 (Protocol Version 4) was considered substantial and included the following changes: the statistical assumptions of the study and the estimated sample size (144 increased to 238 subjects) were updated based on newly published data in a patient population similar to that in the study, which showed that the reduction in Pulmonary Vascular Resistance (PVR) with initial dual combination therapy with macitentan and tadalafil was larger than originally anticipated. In addition, to control for multiplicity, the statistical testing section was updated with the implementation of hierarchical testing for selected secondary endpoints.
01 March 2018	This amendment dated 01 Mar 2018 (Protocol Version 5) was considered non-substantial and included the following changes: monthly testing for liver function was to be performed throughout the study based on a recommendation from the Independent data monitoring committee (IDMC). The order of the hierarchical testing of secondary endpoints was updated (change from baseline to Week 26 in 6-minute walk distance [6MWD] to be tested first) following Food and Drug Administration (FDA) interaction in November 2017.
04 December 2018	This amendment dated 04 Dec 2018 (Protocol Version 6) was considered substantial and included the following change: the dosing instructions for selexipag or placebo study treatment was updated (reduced to once-daily regimen) in the presence of concomitant administration of a moderate CYP2C8 inhibitor based on a drug-drug interaction study with a moderate CYP2C8 inhibitor (example, clopidogrel).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported