Clinical trial results:
AMBITION: A Randomised, Multicenter Study of First-Line Ambrisentan and Tadalafil Combination Therapy in Subjects with Pulmonary Arterial Hypertension

Summary

EudraCT number	2009-011150-17
Trial protocol	NL ES BE SE GB AT GR DE IT FR
Global end of trial date	31 July 2014

Results information

Result version number	v2 (current)
This version publication date	08 April 2016
First version publication date	10 April 2015
Version creation reason	• Correction of full data set Changes required to the EudraCT Results Summary in order to keep consistent with the changes made to the FDAAA Results Summary per the NIH QC review.

Trial information

Trial identification

Sponsor protocol code	AMB112565

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	22 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the difference between two treatment strategies; first-line combination therapy (with ambrisentan 10 mg once daily and tadalafil 40 mg once daily) vs. monotherapy (with ambrisentan 10 mg once daily or tadalafil 40 mg once daily) in participants with pulmonary arterial hypertension (PAH).

Protection of trial subjects:

A gradual titration was put in place in the study, with full dose of tadalafil reached at week 4 and ambrisentan at week 8 – this was intended to minimize the potential for side effects in participants receiving combination therapy.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 October 2010
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	Netherlands: 21
Country: Number of subjects enrolled	Spain: 35
Country: Number of subjects enrolled	Sweden: 21
Country: Number of subjects enrolled	United Kingdom: 29
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	France: 48
Country: Number of subjects enrolled	Germany: 96
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Italy: 44
Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	Canada: 29
Country: Number of subjects enrolled	Japan: 3
Country: Number of subjects enrolled	United States: 248
Worldwide total number of subjects	610
EEA total number of subjects	318

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)	403
From 65 to 84 years	207
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

500 participants (par.) in the ITT Population were also included in the modified ITT Population (those who also met the modified inclusion/exclusion criteria defined in the protocol amendment 2). Disposition results below have been presented for the ITT Population.

Pre-assignment

Screening details:

A total of 610 par. were randomized; however, only 605 were included in the Intent-to-Treat (ITT) Population (randomized par. who received at least one dose of IP). All par. received a minimum of 24 weeks of therapy unless they died or withdrew.

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, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Combination Therapy: Ambrisentan + Tadalafil

Arm description:

Participants initially received one tablet of 5 milligrams (mg) ambrisentan (AMB) and one tablet of AMB matching placebo once daily (QD) for the first 8 weeks plus one tablet of 20 mg tadalafil (TAD) and one tablet of TAD matching placebo QD for the first 4 weeks. The TAD dose was uptitrated to 40 mg (two tablets of 20 mg QD) after 4 weeks and the AMB dose may have been uptitrated to 10 mg (two tablets of 5 mg QD) after 8 weeks. The uptitration of AMB to 10 mg was not mandatory if the investigator decided for tolerability reasons the participants should remain on 5 mg.

Arm type	Experimental
Investigational medicinal product name	ambrisentan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg or 10 mg, once-daily, oral

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

Dosage and administration details:

20 mg or 40 mg once-daily, oral

Arm title	Ambrisentan Monotherapy

Arm description:

Participants initially received one tablet of 5 mg AMB and one tablet of AMB matching placebo QD for the first 8 weeks plus two tablets of TAD matching placebo. The AMB dose may have been uptitrated to 10 mg (two tablets of 5 mg QD) and two tablets of TAD matching placebo after 8 weeks. The uptitration of AMB to 10 mg was not mandatory if the investigator decided for tolerability reasons the participants should remain on 5 mg.

Arm type	Active comparator

Investigational medicinal product name	ambrisentan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg or 10 mg, once-daily, oral

Arm title	Tadalafil Monotherapy

Arm description:

Participants initially received one tablet of 20 mg TAD and one tablet of TAD matching placebo QD for the first 4 weeks plus two tablets of AMB matching placebo. The TAD dose was uptitrated to 40 mg (two tablets of 20 mg QD) and two tablets of AMB matching placebo after 4 weeks.

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

Dosage and administration details:

20 mg or 40 mg once-daily, oral

Number of subjects in period 1[1]	Combination Therapy: Ambrisentan + Tadalafil	Ambrisentan Monotherapy	Tadalafil Monotherapy
Started	302	152	151
Completed	240	108	105
Not completed	62	44	46
Adverse event, serious fatal	9	15	17
Consent withdrawn by subject	10	6	8
Physician decision	14	10	10
Adverse event, non-fatal	25	12	7
Missing Completion Status	1	-	-
Lost to follow-up	2	-	3
Protocol deviation	1	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 610 participants (par.) were randomized; however, only 605 were included in the Intent-to-Treat (ITT) Population (randomized participants who received at least one dose of IP).

Baseline characteristics

Reporting groups	
Reporting group title	Combination Therapy: Ambrisentan + Tadalafil
Reporting group description:	
Participants initially received one tablet of 5 milligrams (mg) ambrisentan (AMB) and one tablet of AMB matching placebo once daily (QD) for the first 8 weeks plus one tablet of 20 mg tadalafil (TAD) and one tablet of TAD matching placebo QD for the first 4 weeks. The TAD dose was uptitrated to 40 mg (two tablets of 20 mg QD) after 4 weeks and the AMB dose may have been uptitrated to 10 mg (two tablets of 5 mg QD) after 8 weeks. The uptitration of AMB to 10 mg was not mandatory if the investigator decided for tolerability reasons the participants should remain on 5 mg.	
Reporting group title	Ambrisentan Monotherapy
Reporting group description:	
Participants initially received one tablet of 5 mg AMB and one tablet of AMB matching placebo QD for the first 8 weeks plus two tablets of TAD matching placebo. The AMB dose may have been uptitrated to 10 mg (two tablets of 5 mg QD) and two tablets of TAD matching placebo after 8 weeks. The uptitration of AMB to 10 mg was not mandatory if the investigator decided for tolerability reasons the participants should remain on 5 mg.	
Reporting group title	Tadalafil Monotherapy
Reporting group description:	
Participants initially received one tablet of 20 mg TAD and one tablet of TAD matching placebo QD for the first 4 weeks plus two tablets of AMB matching placebo. The TAD dose was uptitrated to 40 mg (two tablets of 20 mg QD) and two tablets of AMB matching placebo after 4 weeks.	

Reporting group values	Combination Therapy: Ambrisentan + Tadalafil	Ambrisentan Monotherapy	Tadalafil Monotherapy
Number of subjects	302	152	151
Age categorical Units: Subjects			
Age continuous			
Intent-to-Treat Population			
Units: years			
arithmetic mean	55.9	55.2	55.9
standard deviation	± 13.86	± 14.41	± 14.75
Gender categorical Units: Subjects			
Female	223	117	121
Male	79	35	30
Race Units: Subjects			
African American/African Heritage	11	14	13
American Indian or Alaskan Native	2	0	0
Asian - Central/South Asian Heritage	1	2	1
Asian - Japanese Heritage	3	0	1
Asian - South East Asian Heritage	1	2	1
Native Hawaiian or Other Pacific Islander	1	0	2
White - Arabic /North African Heritage	1	1	0

White - White/Caucasian/European Heritage	280	131	133
Mixed Race	2	1	0
Missing	0	1	0

Reporting group values	Total		
Number of subjects	605		
Age categorical Units: Subjects			

Age continuous			
Intent-to-Treat Population			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	461		
Male	144		
Race Units: Subjects			
African American/African Heritage	38		
American Indian or Alaskan Native	2		
Asian - Central/South Asian Heritage	4		
Asian - Japanese Heritage	4		
Asian - South East Asian Heritage	4		
Native Hawaiian or Other Pacific Islander	3		
White - Arabic /North African Heritage	2		
White - White/Caucasian/European Heritage	544		
Mixed Race	3		
Missing	1		

End points

End points reporting groups

Reporting group title	Combination Therapy: Ambrisentan + Tadalafil

Reporting group description:

Participants initially received one tablet of 5 milligrams (mg) ambrisentan (AMB) and one tablet of AMB matching placebo once daily (QD) for the first 8 weeks plus one tablet of 20 mg tadalafil (TAD) and one tablet of TAD matching placebo QD for the first 4 weeks. The TAD dose was uptitrated to 40 mg (two tablets of 20 mg QD) after 4 weeks and the AMB dose may have been uptitrated to 10 mg (two tablets of 5 mg QD) after 8 weeks. The uptitration of AMB to 10 mg was not mandatory if the investigator decided for tolerability reasons the participants should remain on 5 mg.

Reporting group title	Ambrisentan Monotherapy

Reporting group description:

Participants initially received one tablet of 5 mg AMB and one tablet of AMB matching placebo QD for the first 8 weeks plus two tablets of TAD matching placebo. The AMB dose may have been uptitrated to 10 mg (two tablets of 5 mg QD) and two tablets of TAD matching placebo after 8 weeks. The uptitration of AMB to 10 mg was not mandatory if the investigator decided for tolerability reasons the participants should remain on 5 mg.

Reporting group title	Tadalafil Monotherapy

Reporting group description:

Participants initially received one tablet of 20 mg TAD and one tablet of TAD matching placebo QD for the first 4 weeks plus two tablets of AMB matching placebo. The TAD dose was uptitrated to 40 mg (two tablets of 20 mg QD) and two tablets of AMB matching placebo after 4 weeks.

Subject analysis set title	Monotherapy Pooled: Ambrisentan or Tadalafil
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants initially received one tablet of 5 mg AMB and one tablet of AMB matching placebo QD for the first 8 weeks; or one tablet of 20 mg TAD and one tablet of TAD-matching placebo QD for the first 4 weeks. For participants on TAD, the dose of TAD was uptitrated to 40 mg (two tablets of 20 mg QD) after 4 weeks and for participants on AMB, the dose of AMB may have been uptitrated to 10 mg (two tablets of 5 mg QD) after 8 weeks. The uptitration of AMB to 10 mg was not mandatory if the investigator decided for tolerability reasons the participants should remain on 5 mg.

Primary: Number of participants with first adjudicated clinical failure (CF) event, death, hospitalisation for worsening PAH, disease progression, unsatisfactory long-term clinical response, all through FAV

End point title	Number of participants with first adjudicated clinical failure (CF) event, death, hospitalisation for worsening PAH, disease progression, unsatisfactory long-term clinical response, all through FAV

End point description:

Time to the first adjudicated CF event (death, hospitalization for worsening pulmonary arterial hypertension [PAH], disease progression, or unsatisfactory long-term clinical response) after initiating either first-line combination therapy with AMB and TAD or first-line monotherapy with either drug (AMB or TAD) in par. with PAH was assessed. If data was not available for some par. following a loss to follow-up, their event times were treated as censored at their last assessment time for the statistical analyses. FAV occurred approximately 4 weeks after the predicted 105th adjudicated first CF event was reached. Par. who had an FAV, and who had no adjudicated events or whose first adjudicated event occurred after their FAV, were censored at their individual FAV. Modified Intent-to-Treat (mITT) Population: all randomized par. who met the PAH diagnosis and inclusion/exclusion criteria defined in protocol amendment 2 and who also received at least one dose of investigational product (IP).

End point type	Primary

End point timeframe:

From Baseline up to the Final Assessment Visit (FAV) (average of 609 days)

End point values	Combination Therapy: Ambrisentan + Tadalafil	Ambrisentan Monotherapy	Tadalafil Monotherapy	Monotherapy Pooled: Ambrisentan or Tadalafil
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	253[1]	126[2]	121[3]	247[4]
Units: Participants				
First adjudicated clinical failure event	46	43	34	77
Death (all-cause)	9	2	6	8
Hospitalization for worsening PAH	10	18	12	30
Disease progression	10	12	4	16
Unsatisfactory long-term clinical response	17	11	12	23

Notes:

[1] - mITT Population

[2] - mITT Population

[3] - mITT Population

[4] - mITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Combination Therapy: Ambrisentan + Tadalafil v Monotherapy Pooled: Ambrisentan or Tadalafil
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0002
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.502
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.348
upper limit	0.724

Notes:

[5] - Analysis of time to first adjudicated clinical failure event through FAV. HR is calculated using the Cox proportional hazards model. HR is for Combination Therapy: Ambrisentan + Tadalafil / Monotherapy Pooled: Ambrisentan or Tadalafil.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Combination Therapy: Ambrisentan + Tadalafil v Ambrisentan Monotherapy
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.0004
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.477

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.314
upper limit	0.723

Notes:

[6] - Analysis of time to first adjudicated clinical failure event through FAV. HR is calculated using the Cox proportional hazards model. HR is for Combination Therapy: Ambrisentan + Tadalafil / Ambrisentan Monotherapy.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Combination Therapy: Ambrisentan + Tadalafil v Tadalafil Monotherapy
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.0045
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.528
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.338
upper limit	0.827

Notes:

[7] - Analysis of time to first adjudicated clinical failure event through FAV. HR is calculated using the Cox proportional hazards model. HR is for Combination Therapy: Ambrisentan + Tadalafil / Tadalafil Monotherapy.

Secondary: Percent change from Baseline in the N-Terminal Pro-B-Type Natriuretic Peptide at Week 24

End point title	Percent change from Baseline in the N-Terminal Pro-B-Type Natriuretic Peptide at Week 24

End point description:

N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP) is a surrogate marker of heart failure. The data were log-transformed. The geometric mean was calculated (based on the log-transformed data). The geometric mean ratio was calculated as the ratio between the Week 24 value and the Baseline value (based on the log-transformed data) and presented as percent change = 100 * (geometric mean ratio – 1). The Baseline value is the last value prior to administration of study drug; this may be prior to or on the day of study drug initiation. No imputation was performed for missing data. The secondary endpoints were analyzed according to a pre-specified hierarchical testing procedure.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Combination Therapy: Ambrisentan + Tadalafil	Ambrisentan Monotherapy	Tadalafil Monotherapy	Monotherapy Pooled: Ambrisentan or Tadalafil
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	204[8]	126[9]	121[10]	247[11]
Units: Percent change				
arithmetic mean (standard error)	-67.15 (±	-50.37 (±	-56.15 (±	-43.83 (±

	0.069)	0.07)	0.096)	0.095)

Notes:

[8] - mITT Population. Only participants with data available at the specified time points were analyzed.

[9] - mITT Population. Only participants with data available at the specified time points were analyzed.

[10] - mITT Population. Only participants with data available at the specified time points were analyzed.

[11] - mITT Population. Only participants with data available at the specified time points were analyzed.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Combination Therapy: Ambrisentan + Tadalafil v Monotherapy Pooled: Ambrisentan or Tadalafil
Number of subjects included in analysis	451
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean Percent Difference
Point estimate	-33.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-44.78
upper limit	-20.66

Notes:

[12] - Mean percent difference is for Combination Therapy: Ambrisentan + Tadalafil - Monotherapy Pooled: Ambrisentan or Tadalafil.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Combination Therapy: Ambrisentan + Tadalafil v Ambrisentan Monotherapy
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.0111
Method	ANCOVA
Parameter estimate	Mean Percent Difference
Point estimate	-25.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.04
upper limit	-6.4

Notes:

[13] - Mean percent difference is for Combination Therapy: Ambrisentan + Tadalafil - Ambrisentan Monotherapy.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Combination Therapy: Ambrisentan + Tadalafil v Tadalafil Monotherapy

Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean Percent Difference
Point estimate	-41.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.16
upper limit	-26.97

Notes:

[14] - Mean percent difference is for Combination Therapy: Ambrisentan + Tadalafil - Tadalafil Monotherapy.

Secondary: Percentage of participants with a satisfactory clinical response at Week 24

End point title	Percentage of participants with a satisfactory clinical response at Week 24

End point description:

A satisfactory clinical response at Week 24 is defined as a participant who meets all of the following criteria: 10% improvement in 6MWD compared with Baseline; improvement to or maintenance of World Health Organization (WHO) class I or II symptoms; no events of clinical worsening prior to or at the Week 24 visit. Clinical worsening events included: death, hospitalization for pulmonary arterial hypertension (PAH), and disease progression. Participants without an event of clinical worsening prior to or at the Week 24 visit who did not have a 6MWD value or a WHO functional class value at Week 24 were excluded from the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Combination Therapy: Ambrisentan + Tadalafil	Ambrisentan Monotherapy	Tadalafil Monotherapy	Monotherapy Pooled: Ambrisentan or Tadalafil
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	234[15]	113[16]	113[17]	226[18]
Units: Percentage of participants	39	31	27	29

Notes:

[15] - mITT Population. Only those participants who had a "Yes"/"No" response were analyzed.

[16] - mITT Population. Only those participants who had a "Yes"/"No" response were analyzed.

[17] - mITT Population. Only those participants who had a "Yes"/"No" response were analyzed.

[18] - mITT Population. Only those participants who had a "Yes"/"No" response were analyzed.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Combination Therapy: Ambrisentan + Tadalafil v Monotherapy Pooled: Ambrisentan or Tadalafil

Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.0264
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.563
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.054
upper limit	2.319

Notes:

[19] - Odds ratio is for Combination Therapy: Ambrisentan + Tadalafil / Monotherapy Pooled: Ambrisentan or Tadalafil.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Combination Therapy: Ambrisentan + Tadalafil v Ambrisentan Monotherapy
Number of subjects included in analysis	347
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.1518
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.424
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.878
upper limit	2.308

Notes:

[20] - Odds ratio is for Combination Therapy: Ambrisentan + Tadalafil / Ambrisentan Monotherapy.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Combination Therapy: Ambrisentan + Tadalafil v Tadalafil Monotherapy
Number of subjects included in analysis	347
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.0321
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.723
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.047
upper limit	2.833

Notes:

[21] - Odds ratio is for Combination Therapy: Ambrisentan + Tadalafil / Tadalafil Monotherapy.

Secondary: Change from Baseline in the 6 minute walk distance test at Week 24

End point title	Change from Baseline in the 6 minute walk distance test at Week 24

End point description:

The 6-minute walk distance (6MWD) test measures the distance that a participant can walk in a period of 6 minutes. Change from Baseline was calculated as the Week 24 value minus the Baseline value. The analysis was performed based on last observation carried forward data, except in the case of an adjudicated clinical failure event of death or hospitalization preceding the missing data observation. In this case, the missing observation was assigned the worst-rank score relative to those actually observed and was assigned a rank reflecting the relative order of the actual event times. Baseline 6MWD comprised of an average of the last two consecutive measurements prior to randomization that varied by no greater than 10%. If only one measurement was available, that measurement was used. If no two consecutive measures vary by no greater than 10% then Baseline was based on the last two consecutive measures for a participant.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Combination Therapy: Ambrisentan + Tadalafil	Ambrisentan Monotherapy	Tadalafil Monotherapy	Monotherapy Pooled: Ambrisentan or Tadalafil
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	248[22]	124[23]	120[24]	244[25]
Units: Meters				
median (confidence interval 95%)	48.98 (39 to 57.5)	27 (12.5 to 38)	22.7 (16.5 to 35.5)	23.8 (19 to 33.5)

Notes:

[22] - mITT Population. Only participants with Baseline data were analyzed.

[23] - mITT Population. Only participants with Baseline data were analyzed.

[24] - mITT Population. Only participants with Baseline data were analyzed.

[25] - mITT Population. Only participants with Baseline data were analyzed.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Combination Therapy: Ambrisentan + Tadalafil v Monotherapy Pooled: Ambrisentan or Tadalafil
Number of subjects included in analysis	492
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	< 0.0001
Method	Stratified Wilcoxon Rank Sum Test
Parameter estimate	Median Difference
Point estimate	22.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	12
upper limit	33.5

Notes:

[26] - Median difference is for Combination Therapy: Ambrisentan + Tadalafil - Monotherapy Pooled: Ambrisentan or Tadalafil.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Combination Therapy: Ambrisentan + Tadalafil v Ambrisentan Monotherapy
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	= 0.0005
Method	Stratified Wilcoxon Rank Sum Test
Parameter estimate	Median Difference
Point estimate	24.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	11
upper limit	38.5

Notes:

[27] - Median difference is for Combination Therapy: Ambrisentan + Tadalafil - Ambrisentan Monotherapy.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Combination Therapy: Ambrisentan + Tadalafil v Tadalafil Monotherapy
Number of subjects included in analysis	368
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.003
Method	Stratified Wilcoxon Rank Sum Test
Parameter estimate	Median Difference
Point estimate	20.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	8
upper limit	33.7

Notes:

[28] - Median difference is for Combination Therapy: Ambrisentan + Tadalafil - Tadalafil Monotherapy.

Secondary: Change from Baseline in the World Health Organization Functional Class at Week 24

End point title	Change from Baseline in the World Health Organization Functional Class at Week 24

End point description:

The WHO Functional Class (FC) indicates the severity of PAH and is an adaptation of the New York Heart Association classification. It was assessed by the investigator. There are four grades for WHO FC based on severity of symptoms (Class I = none, Class IV = most severe). Baseline WHO FC is the latest assessment prior to dosing (i.e., at Randomization or Screening). Change from Baseline at Week 24 was calculated as the Week 24 value minus the Baseline value. The analysis was performed based on the last observation carried forward data, except in the case of an adjudicated clinical failure event of death or hospitalization preceding the missing data observation. In this case, the missing observations was assigned the worst-rank score relative to those actually observed and was assigned rank reflecting the relative order of the actual event times.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Combination Therapy: Ambrisentan + Tadalafil	Ambrisentan Monotherapy	Tadalafil Monotherapy	Monotherapy Pooled: Ambrisentan or Tadalafil
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	252[29]	124[30]	120[31]	244[32]
Units: Scores on a scale				
median (inter-quartile range (Q1-Q3))	0 (-1 to 0)	0 (-1 to 0)	0 (-1 to 0)	0 (-1 to 0)

Notes:

[29] - mITT Population. Only participants with Baseline data were analyzed.

[30] - mITT Population. Only participants with Baseline data were analyzed.

[31] - mITT Population. Only participants with Baseline data were analyzed.

[32] - mITT Population. Only participants with Baseline data were analyzed.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Combination Therapy: Ambrisentan + Tadalafil v Monotherapy Pooled: Ambrisentan or Tadalafil
Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.2287
Method	Stratified Wilcoxon Rank Sum Test
Parameter estimate	Median Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Notes:

[33] - Median difference is for Combination Therapy: Ambrisentan + Tadalafil - Monotherapy Pooled: Ambrisentan or Tadalafil.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
This comparison was not formally tested according to the pre-defined hierarchical testing procedure.	
Comparison groups	Combination Therapy: Ambrisentan + Tadalafil v Ambrisentan Monotherapy
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority[34]
Method	Stratified Wilcoxon Rank Sum Test
Parameter estimate	Median Difference
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Notes:

[34] - Median difference is for Combination Therapy: Ambrisentan + Tadalafil - Ambrisentan Monotherapy.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

This comparison was not formally tested according to the pre-defined hierarchical testing procedure.

Comparison groups	Combination Therapy: Ambrisentan + Tadalafil v Tadalafil Monotherapy
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority[35]
Method	Stratified Wilcoxon Rank Sum Test
Parameter estimate	Median Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Notes:

[35] - Median difference is for Combination Therapy: Ambrisentan + Tadalafil - Tadalafil Monotherapy.

Secondary: Change from Baseline in Borg Dyspnea Index at Week 24

End point title	Change from Baseline in Borg Dyspnea Index at Week 24

End point description:

Borg Dyspnea Index (BDI) indicates the degree of breathlessness after completion of the 6 minute walk test. The BDI was calculated by using the Borg category (C) ratio (R) CR10 scale which starts at 0 (nothing at all) and has no upper limit (extremely strong). Change from BL was calculated as the Week 24 values minus the BL value. The BDI scale was assessed by each participant. The BL BDI score is the average of the two BDI values obtained following the two 6MWD tests used in determining the BL 6MWD. A negative change from BL in the BDI score represented an improvement for the participant. The analysis was performed based on the last observation carried forward data, except in the case of an adjudicated clinical failure event of death or hospitalization preceding the missing data observation. In this case, the missing observation was assigned the worst-rank score relative to those actually observed and was assigned rank reflecting the relative order of the actual event times.

End point type	Secondary

End point timeframe:

Baseline (BL) and Week 24

End point values	Combination Therapy: Ambrisentan + Tadalafil	Ambrisentan Monotherapy	Tadalafil Monotherapy	Monotherapy Pooled: Ambrisentan or Tadalafil
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	247[36]	124[37]	120[38]	244[39]
Units: Scores on a scale				

median (inter-quartile range (Q1-Q3))	-1 (-2 to 0.5)	-0.5 (-1.5 to 0.5)	-0.5 (-2 to 0.88)	-0.5 (-1.5 to 0.5)

Notes:

[36] - mITT Population. Only participants with Baseline data were analyzed.

[37] - mITT Population. Only participants with Baseline data were analyzed.

[38] - mITT Population. Only participants with Baseline data were analyzed.

[39] - mITT Population. Only participants with Baseline data were analyzed.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

This endpoint was not formally tested according to the pre-defined hierarchical testing procedure.

Comparison groups	Combination Therapy: Ambrisentan + Tadalafil v Monotherapy Pooled: Ambrisentan or Tadalafil
Number of subjects included in analysis	491
Analysis specification	Pre-specified
Analysis type	superiority[40]
Method	Stratified Wilcoxon Rank Sum Test
Parameter estimate	Median Difference
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.75
upper limit	0

Notes:

[40] - Median difference is for Combination Therapy: Ambrisentan + Tadalafil - Monotherapy Pooled: Ambrisentan or Tadalafil.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

This endpoint was not formally tested according to the pre-defined hierarchical testing procedure.

Comparison groups	Combination Therapy: Ambrisentan + Tadalafil v Ambrisentan Monotherapy
Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	superiority[41]
Method	Stratified Wilcoxon Rank Sum Test
Parameter estimate	Median Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Notes:

[41] - Median difference is for Combination Therapy: Ambrisentan + Tadalafil - Ambrisentan Monotherapy.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

This endpoint was not formally tested according to the pre-defined hierarchical testing procedure.

Comparison groups	Combination Therapy: Ambrisentan + Tadalafil v Tadalafil

	Monotherapy
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	superiority[42]
Method	Stratified Wilcoxon Rank Sum Test
Parameter estimate	Median Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Notes:

[42] - Median difference is for Combination Therapy: Ambrisentan + Tadalafil - Tadalafil Monotherapy.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious AEs were collected from the start of investigational product until 30 days after the last dose of investigational product (average of 639 days on investigational product).

Adverse event reporting additional description:

SAEs and non-serious AEs were collected in members of the Safety Population, comprised of all randomized participants who received at least one dose of investigational product. Only AEs for the "On-Randomized Treatment" arms are tabulated.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Combination Therapy: Ambrisentan + Tadalafil

Reporting group description:

Participants initially received one tablet of 5 milligrams (mg) ambrisentan (AMB) and one tablet of AMB matching placebo once daily (QD) for the first 8 weeks plus one tablet of 20 mg tadalafil (TAD) and one tablet of TAD matching placebo QD for the first 4 weeks. The TAD dose was uptitrated to 40 mg (two tablets of 20 mg QD) after 4 weeks and the AMB dose may have been uptitrated to 10 mg (two tablets of 5 mg QD) after 8 weeks. The uptitration of AMB to 10 mg was not mandatory if the investigator decided for tolerability reasons the participants should remain on 5 mg.

Reporting group title	Tadalafil Monotherapy

Reporting group description:

Participants initially received one tablet of 20 mg TAD and one tablet of TAD matching placebo QD for the first 4 weeks plus two tablets of AMB matching placebo. The TAD dose was uptitrated to 40 mg (two tablets of 20 mg QD) and two tablets of AMB matching placebo after 4 weeks.

Reporting group title	Ambrisentan Monotherapy

Reporting group description:

Participants initially received one tablet of 5 mg AMB and one tablet of AMB matching placebo QD for the first 8 weeks plus two tablets of TAD matching placebo. The AMB dose may have been uptitrated to 10 mg (two tablets of 5 mg QD) and two tablets of TAD matching placebo after 8 weeks. The uptitration of AMB to 10 mg was not mandatory if the investigator decided for tolerability reasons the participants should remain on 5 mg.

Serious adverse events	Combination Therapy: Ambrisentan + Tadalafil	Tadalafil Monotherapy	Ambrisentan Monotherapy
Total subjects affected by serious adverse events			
subjects affected / exposed	124 / 302 (41.06%)	68 / 151 (45.03%)	63 / 152 (41.45%)
number of deaths (all causes)	29	22	19
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			

subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Adenocarcinoma of the cervix			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Basal cell carcinoma			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon adenoma			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Colon cancer			
subjects affected / exposed	2 / 302 (0.66%)	0 / 151 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukaemia			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Lipoma			

subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Lung neoplasm			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Metastases to liver			
subjects affected / exposed	2 / 302 (0.66%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metastatic neoplasm			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Pancreatic carcinoma stage IV			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Prostate cancer			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Salivary gland neoplasm			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Thyroid cancer			

subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Uterine cancer			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Hypertension			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Hypotension			
subjects affected / exposed	3 / 302 (0.99%)	2 / 151 (1.32%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	2 / 3	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian artery stenosis			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular insufficiency			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Venous thrombosis limb			

subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Chest discomfort			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 302 (0.00%)	2 / 151 (1.32%)	0 / 152 (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
Death			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Drug withdrawal syndrome			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Euthanasia			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Generalised oedema			

subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Infusion site phlebitis			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Non-cardiac chest pain			
subjects affected / exposed	7 / 302 (2.32%)	0 / 151 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	5 / 302 (1.66%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	3 / 5	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	4 / 302 (1.32%)	1 / 151 (0.66%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Immune system disorders			
Autoimmune disorder			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Reproductive system and breast disorders			
Ovarian cyst ruptured			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Prostatitis			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Vaginal haemorrhage			
subjects affected / exposed	2 / 302 (0.66%)	0 / 151 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	3 / 302 (0.99%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Atelectasis			
subjects affected / exposed	2 / 302 (0.66%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 302 (0.33%)	1 / 151 (0.66%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic respiratory failure			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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

Dyspnoea			
subjects affected / exposed	10 / 302 (3.31%)	4 / 151 (2.65%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	3 / 10	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Haemoptysis			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoventilation			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	2 / 302 (0.66%)	1 / 151 (0.66%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Lung disorder			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Obliterative bronchiolitis			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Organising pneumonia			

subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	4 / 302 (1.32%)	2 / 151 (1.32%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	2 / 5	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pleurisy			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Pleuritic pain			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Pneumonia aspiration			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Pneumothorax spontaneous			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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 arterial hypertension			
subjects affected / exposed	2 / 302 (0.66%)	1 / 151 (0.66%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary embolism			
subjects affected / exposed	3 / 302 (0.99%)	2 / 151 (1.32%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary fibrosis			

subjects affected / exposed	0 / 302 (0.00%)	2 / 151 (1.32%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	11 / 302 (3.64%)	12 / 151 (7.95%)	16 / 152 (10.53%)
occurrences causally related to treatment / all	0 / 12	0 / 12	0 / 17
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Pulmonary oedema			
subjects affected / exposed	4 / 302 (1.32%)	0 / 151 (0.00%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	1 / 4	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary vasculitis			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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 distress			
subjects affected / exposed	1 / 302 (0.33%)	1 / 151 (0.66%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	5 / 302 (1.66%)	1 / 151 (0.66%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep apnoea syndrome			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Depression			

subjects affected / exposed	1 / 302 (0.33%)	1 / 151 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Suicidal ideation			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Investigations			
Blood potassium decreased			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure systolic increased			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Oxygen saturation decreased			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Transaminases increased			
subjects affected / exposed	2 / 302 (0.66%)	0 / 151 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Burns second degree			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Concussion			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 302 (0.33%)	1 / 151 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Hip fracture			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Lower limb fracture			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mountain sickness acute			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Muscle injury			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Muscle rupture			

subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Post procedural complication			
subjects affected / exposed	1 / 302 (0.33%)	1 / 151 (0.66%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural myocardial infarction			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation pneumonitis			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory fume inhalation disorder			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Spinal fracture			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Subdural haematoma			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Tendon rupture			

subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Toxicity to various agents			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic ulcer			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Upper limb fracture			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	2 / 302 (0.66%)	0 / 151 (0.00%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Arrhythmia supraventricular			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Atrial fibrillation			

subjects affected / exposed	1 / 302 (0.33%)	3 / 151 (1.99%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	3 / 302 (0.99%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Atrioventricular block complete			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Atrioventricular block second degree			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Bradycardia			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Cardiac arrest			
subjects affected / exposed	2 / 302 (0.66%)	2 / 151 (1.32%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
Cardiac disorder			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Cardiac failure			

subjects affected / exposed	6 / 302 (1.99%)	3 / 151 (1.99%)	6 / 152 (3.95%)
occurrences causally related to treatment / all	1 / 7	1 / 3	1 / 7
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Cardiac failure acute			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Cardiac failure congestive			
subjects affected / exposed	3 / 302 (0.99%)	1 / 151 (0.66%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	2 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiorenal syndrome			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cor pulmonale			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Cor pulmonale acute			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Coronary artery occlusion			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Coronary artery stenosis			
subjects affected / exposed	2 / 302 (0.66%)	0 / 151 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			

subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Myocardial infarction			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Nodal arrhythmia			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Palpitations			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Pleuropericarditis			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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	5 / 302 (1.66%)	3 / 151 (1.99%)	8 / 152 (5.26%)
occurrences causally related to treatment / all	2 / 7	0 / 3	1 / 8
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Supraventricular extrasystoles			

subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Supraventricular tachyarrhythmia			
subjects affected / exposed	2 / 302 (0.66%)	0 / 151 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 302 (0.00%)	2 / 151 (1.32%)	0 / 152 (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
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Carotid artery stenosis			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Convulsion			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Dizziness			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Headache			

subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Ischaemic stroke			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 302 (0.33%)	1 / 151 (0.66%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Restless legs syndrome			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Somnolence			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Syncope			
subjects affected / exposed	9 / 302 (2.98%)	7 / 151 (4.64%)	5 / 152 (3.29%)
occurrences causally related to treatment / all	4 / 10	0 / 7	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 302 (3.31%)	5 / 151 (3.31%)	3 / 152 (1.97%)
occurrences causally related to treatment / all	1 / 12	2 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia macrocytic			

subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Hyperchromic anaemia			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Hypochromic anaemia			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Iron deficiency anaemia			
subjects affected / exposed	2 / 302 (0.66%)	0 / 151 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Spontaneous haematoma			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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			
Sudden hearing loss			
subjects affected / exposed	2 / 302 (0.66%)	0 / 151 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			

subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Retinal vein occlusion			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia			
subjects affected / exposed	1 / 302 (0.33%)	1 / 151 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Abdominal pain upper			
subjects affected / exposed	1 / 302 (0.33%)	1 / 151 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Duodenogastric reflux			

subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Epiploic appendagitis			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Gastric ulcer			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Gastritis			
subjects affected / exposed	2 / 302 (0.66%)	0 / 151 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Gastrointestinal angiodysplasia			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 302 (0.99%)	1 / 151 (0.66%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal inflammation			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 302 (0.33%)	2 / 151 (1.32%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Hiatus hernia			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	2 / 302 (0.66%)	1 / 151 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal ulcer			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Melaena			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Oesophageal haemorrhage			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Pancreatitis			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Rectal haemorrhage			

subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	1 / 302 (0.33%)	1 / 151 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Biliary colic			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Cholecystitis			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Cholecystitis chronic			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Cholelithiasis			

subjects affected / exposed	2 / 302 (0.66%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis acute			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Rash			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Skin ulcer			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	2 / 302 (0.66%)	1 / 151 (0.66%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			

subjects affected / exposed	3 / 302 (0.99%)	1 / 151 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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			
Arthritis			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Back pain			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chondromalacia			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Connective tissue disorder			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Intervertebral disc disorder			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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 / 302 (0.33%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Juvenile idiopathic arthritis			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Mixed connective tissue disease			
subjects affected / exposed	1 / 302 (0.33%)	1 / 151 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myopathy			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Myositis			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			

subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Osteonecrosis			
subjects affected / exposed	2 / 302 (0.66%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periarthritis			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic sclerosis			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Alveolar osteitis			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial pyelonephritis			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Bronchitis			
subjects affected / exposed	1 / 302 (0.33%)	3 / 151 (1.99%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis viral			

subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site cellulitis			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Catheter site infection			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Cellulitis			
subjects affected / exposed	2 / 302 (0.66%)	3 / 151 (1.99%)	5 / 152 (3.29%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Conjunctivitis viral			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Erysipelas			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia infection			

subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Gastroenteritis			
subjects affected / exposed	2 / 302 (0.66%)	0 / 151 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis C			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Herpes zoster			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Infection			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 302 (0.33%)	1 / 151 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			

subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Lower respiratory tract			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Lung infection			
subjects affected / exposed	3 / 302 (0.99%)	1 / 151 (0.66%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising fasciitis			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Pneumonia			
subjects affected / exposed	15 / 302 (4.97%)	7 / 151 (4.64%)	10 / 152 (6.58%)
occurrences causally related to treatment / all	0 / 16	0 / 8	0 / 10
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Postoperative wound infection			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Pyelonephritis			

subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Respiratory tract infection			
subjects affected / exposed	4 / 302 (1.32%)	1 / 151 (0.66%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 302 (0.33%)	3 / 151 (1.99%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 302 (0.33%)	2 / 151 (1.32%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 302 (0.66%)	1 / 151 (0.66%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vaginal infection			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Viral infection			

subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
West Nile viral infection			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 302 (0.33%)	1 / 151 (0.66%)	2 / 152 (1.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Diabetic ketoacidosis			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Fluid overload			
subjects affected / exposed	5 / 302 (1.66%)	4 / 151 (2.65%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	2 / 6	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid retention			

subjects affected / exposed	3 / 302 (0.99%)	0 / 151 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 302 (0.33%)	0 / 151 (0.00%)	0 / 152 (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
Hypovolaemia			
subjects affected / exposed	0 / 302 (0.00%)	0 / 151 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic syndrome			
subjects affected / exposed	0 / 302 (0.00%)	1 / 151 (0.66%)	0 / 152 (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

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

Non-serious adverse events	Combination Therapy: Ambrisentan + Tadalafil	Tadalafil Monotherapy	Ambrisentan Monotherapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	279 / 302 (92.38%)	135 / 151 (89.40%)	140 / 152 (92.11%)
Vascular disorders			
Flushing			
subjects affected / exposed	41 / 302 (13.58%)	15 / 151 (9.93%)	18 / 152 (11.84%)
occurrences (all)	44	16	18
Hypotension			
subjects affected / exposed	21 / 302 (6.95%)	9 / 151 (5.96%)	8 / 152 (5.26%)
occurrences (all)	25	10	8
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	9 / 302 (2.98%)	8 / 151 (5.30%)	4 / 152 (2.63%)
occurrences (all)	9	8	4
Chest discomfort			
subjects affected / exposed	16 / 302 (5.30%)	5 / 151 (3.31%)	6 / 152 (3.95%)
occurrences (all)	18	6	6
Fatigue			
subjects affected / exposed	35 / 302 (11.59%)	20 / 151 (13.25%)	22 / 152 (14.47%)
occurrences (all)	42	22	26
Non-cardiac chest pain			
subjects affected / exposed	26 / 302 (8.61%)	9 / 151 (5.96%)	14 / 152 (9.21%)
occurrences (all)	31	9	17
Oedema peripheral			
subjects affected / exposed	133 / 302 (44.04%)	44 / 151 (29.14%)	60 / 152 (39.47%)
occurrences (all)	184	55	82
Pain			
subjects affected / exposed	8 / 302 (2.65%)	8 / 151 (5.30%)	2 / 152 (1.32%)
occurrences (all)	8	8	2
Pyrexia			
subjects affected / exposed	17 / 302 (5.63%)	2 / 151 (1.32%)	6 / 152 (3.95%)
occurrences (all)	22	2	6
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	53 / 302 (17.55%)	25 / 151 (16.56%)	20 / 152 (13.16%)
occurrences (all)	62	28	25
Dyspnoea			
subjects affected / exposed	46 / 302 (15.23%)	28 / 151 (18.54%)	27 / 152 (17.76%)
occurrences (all)	61	39	32
Epistaxis			
subjects affected / exposed	27 / 302 (8.94%)	15 / 151 (9.93%)	7 / 152 (4.61%)
occurrences (all)	32	18	7
Nasal congestion			
subjects affected / exposed	58 / 302 (19.21%)	17 / 151 (11.26%)	25 / 152 (16.45%)
occurrences (all)	69	20	34
Oropharyngeal pain			

subjects affected / exposed	7 / 302 (2.32%)	9 / 151 (5.96%)	9 / 152 (5.92%)
occurrences (all)	9	11	9
Sinus congestion			
subjects affected / exposed	18 / 302 (5.96%)	4 / 151 (2.65%)	9 / 152 (5.92%)
occurrences (all)	19	5	9
Psychiatric disorders			
Depression			
subjects affected / exposed	13 / 302 (4.30%)	8 / 151 (5.30%)	3 / 152 (1.97%)
occurrences (all)	15	8	3
Insomnia			
subjects affected / exposed	21 / 302 (6.95%)	10 / 151 (6.62%)	6 / 152 (3.95%)
occurrences (all)	23	11	7
Cardiac disorders			
Palpitations			
subjects affected / exposed	33 / 302 (10.93%)	20 / 151 (13.25%)	22 / 152 (14.47%)
occurrences (all)	40	20	25
Nervous system disorders			
Dizziness			
subjects affected / exposed	62 / 302 (20.53%)	22 / 151 (14.57%)	31 / 152 (20.39%)
occurrences (all)	71	29	35
Headache			
subjects affected / exposed	124 / 302 (41.06%)	55 / 151 (36.42%)	51 / 152 (33.55%)
occurrences (all)	149	69	69
Presyncope			
subjects affected / exposed	11 / 302 (3.64%)	11 / 151 (7.28%)	6 / 152 (3.95%)
occurrences (all)	12	12	6
Syncope			
subjects affected / exposed	9 / 302 (2.98%)	8 / 151 (5.30%)	4 / 152 (2.63%)
occurrences (all)	11	9	7
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	38 / 302 (12.58%)	11 / 151 (7.28%)	8 / 152 (5.26%)
occurrences (all)	39	12	8
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	5 / 302 (1.66%)	8 / 151 (5.30%)	6 / 152 (3.95%)
occurrences (all)	5	10	8

Eye disorders			
Vision blurred			
subjects affected / exposed	19 / 302 (6.29%)	4 / 151 (2.65%)	8 / 152 (5.26%)
occurrences (all)	20	4	8
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	4 / 302 (1.32%)	11 / 151 (7.28%)	8 / 152 (5.26%)
occurrences (all)	4	13	8
Abdominal pain			
subjects affected / exposed	9 / 302 (2.98%)	7 / 151 (4.64%)	9 / 152 (5.92%)
occurrences (all)	9	10	9
Abdominal pain upper			
subjects affected / exposed	8 / 302 (2.65%)	8 / 151 (5.30%)	6 / 152 (3.95%)
occurrences (all)	8	8	8
Constipation			
subjects affected / exposed	17 / 302 (5.63%)	6 / 151 (3.97%)	10 / 152 (6.58%)
occurrences (all)	20	6	11
Diarrhoea			
subjects affected / exposed	63 / 302 (20.86%)	26 / 151 (17.22%)	35 / 152 (23.03%)
occurrences (all)	84	36	49
Dry mouth			
subjects affected / exposed	8 / 302 (2.65%)	3 / 151 (1.99%)	11 / 152 (7.24%)
occurrences (all)	8	3	11
Dyspepsia			
subjects affected / exposed	32 / 302 (10.60%)	18 / 151 (11.92%)	6 / 152 (3.95%)
occurrences (all)	35	22	6
Gastrooesophageal reflux disease			
subjects affected / exposed	23 / 302 (7.62%)	15 / 151 (9.93%)	10 / 152 (6.58%)
occurrences (all)	25	20	10
Nausea			
subjects affected / exposed	47 / 302 (15.56%)	23 / 151 (15.23%)	23 / 152 (15.13%)
occurrences (all)	61	29	31
Vomiting			
subjects affected / exposed	35 / 302 (11.59%)	13 / 151 (8.61%)	13 / 152 (8.55%)
occurrences (all)	42	16	19
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	13 / 302 (4.30%)	6 / 151 (3.97%)	10 / 152 (6.58%)
occurrences (all)	13	6	10
Rash			
subjects affected / exposed	24 / 302 (7.95%)	5 / 151 (3.31%)	6 / 152 (3.95%)
occurrences (all)	29	8	7
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	41 / 302 (13.58%)	23 / 151 (15.23%)	21 / 152 (13.82%)
occurrences (all)	58	24	32
Back pain			
subjects affected / exposed	43 / 302 (14.24%)	23 / 151 (15.23%)	17 / 152 (11.18%)
occurrences (all)	52	24	19
Muscle spasms			
subjects affected / exposed	25 / 302 (8.28%)	10 / 151 (6.62%)	8 / 152 (5.26%)
occurrences (all)	28	11	10
Myalgia			
subjects affected / exposed	30 / 302 (9.93%)	18 / 151 (11.92%)	12 / 152 (7.89%)
occurrences (all)	35	23	13
Neck pain			
subjects affected / exposed	10 / 302 (3.31%)	8 / 151 (5.30%)	4 / 152 (2.63%)
occurrences (all)	12	12	4
Pain in extremity			
subjects affected / exposed	49 / 302 (16.23%)	22 / 151 (14.57%)	16 / 152 (10.53%)
occurrences (all)	61	27	19
Infections and infestations			
Bronchitis			
subjects affected / exposed	34 / 302 (11.26%)	10 / 151 (6.62%)	7 / 152 (4.61%)
occurrences (all)	44	11	13
Influenza			
subjects affected / exposed	14 / 302 (4.64%)	7 / 151 (4.64%)	9 / 152 (5.92%)
occurrences (all)	18	8	10
Nasopharyngitis			
subjects affected / exposed	51 / 302 (16.89%)	24 / 151 (15.89%)	32 / 152 (21.05%)
occurrences (all)	87	46	60
Sinusitis			

subjects affected / exposed	22 / 302 (7.28%)	11 / 151 (7.28%)	11 / 152 (7.24%)
occurrences (all)	36	15	16
Upper respiratory tract infection			
subjects affected / exposed	41 / 302 (13.58%)	22 / 151 (14.57%)	23 / 152 (15.13%)
occurrences (all)	60	26	29
Urinary tract infection			
subjects affected / exposed	24 / 302 (7.95%)	18 / 151 (11.92%)	12 / 152 (7.89%)
occurrences (all)	25	24	13
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	10 / 302 (3.31%)	8 / 151 (5.30%)	9 / 152 (5.92%)
occurrences (all)	11	9	10
Fluid retention			
subjects affected / exposed	16 / 302 (5.30%)	9 / 151 (5.96%)	7 / 152 (4.61%)
occurrences (all)	19	10	7
Hypokalaemia			
subjects affected / exposed	17 / 302 (5.63%)	5 / 151 (3.31%)	8 / 152 (5.26%)
occurrences (all)	26	5	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 August 2010	• Clarified primary endpoint component of unsatisfactory long-term clinical response (that 2 WHO FC III symptoms to be 6 months apart rather than sustained for 6 months) • Highlighted screening and Baseline 6MWD test values must not vary by more than 10%. • Revised exclusion criteria to prohibit concomitant use of cyclosporine A. • Clarified the options for dosage following a clinical failure event • Potential Hy's law/liver event definitions amended for consistency with other liver event definitions; clarified protocol defined serious adverse events (SAEs) and reporting timelines. • Revised Appendix 2 to align withholding of IP and nitrates with the rest of the protocol.
17 November 2011	• Primary endpoint wording clarified for hospitalization due to PAH to include both elective and non-elective hospitalizations. • Increased sample size, recruitment, and study duration, and removed the interim analyses, to increase the power of comparison. • Revised inclusion/exclusion criteria to reduce the number of subjects with multiple left heart disease risk factors. • Added "As treated" population for safety data. • Clarified to permit use of cyclosporine (ophthalmic formulation) • Allowed use of local laboratory tests at screening • Revised inclusion criteria to allow the use of right heart catheterization (RHC) in limited circumstances (applicable only in the US). • Updated testing and ordering of secondary endpoints.
30 May 2012	• Added modified Intent-to-Treat (mITT) population for the primary analysis based on inclusion criteria in Amendment 2, including an increase in sample size and duration to retain power for mITT analysis. • Revised exclusion criteria for previous PAH therapies and nitrate use. • Changed liver-event stopping criteria to allow stopping of ambrisentan/placebo only.
19 March 2013	• Increased sample size due to lower than anticipated (blinded) event rate. • Clarified the wording of the primary endpoint component of unsatisfactory long-term clinical response to indicate that subjects needed to only have taken one dose of randomized treatment and not been on randomized treatment for 6 months.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported