



Clinical trial results:

Effects of combination of bosentan and sildenafil versus sildenafil monotherapy on morbidity and mortality in symptomatic patients with pulmonary arterial hypertension – A multicenter, double - blind, randomized, placebo - controlled, parallel group, prospective, event driven Phase IV study

"Efectos de la combinación de bosentan y sildenafil frente a sildenafil en monoterapia sobre la morbimortalidad en pacientes sintomáticos con hipertensión arterial pulmonar – Estudio de fase IV, multicéntrico, en doble ciego, aleatorizado, controlado con placebo, de grupos paralelos, prospectivo y basado en acontecimientos."

Summary

EudraCT number	2005-005068-97
Trial protocol	DE SE DK GB ES PT GR BE CZ SK
Global end of trial date	05 December 2013

Results information

Result version number	v1 (current)
This version publication date	10 December 2016
First version publication date	10 December 2016

Trial information

Trial identification

Sponsor protocol code	AC-052-414
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00303459
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, 4123
Public contact	Loic Perchenet, Actelion Pharmaceuticals Ltd, loic.perchenet@actelion.com
Scientific contact	Loic Perchenet, Actelion Pharmaceuticals Ltd, loic.perchenet@actelion.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No
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Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 December 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 December 2013
Global end of trial reached?	Yes
Global end of trial date	05 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To demonstrate that the combination of bosentan and sildenafil prolongs the time to the first adjudicated morbidity/mortality event compared with sildenafil monotherapy in symptomatic patients with pulmonary arterial hypertension (PAH)

Protection of trial subjects:

The clinical trial was designed and conducted in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations, including the European Directive 2001/20/EC, the US CFR Title 21 (adapt to the countries where the trial was conducted), and with the ethical principles laid down in the Declaration of Helsinki

Background therapy:

PDE5-i at stable dose for 3 months prior to randomization

Evidence for comparator: -

Actual start date of recruitment	17 May 2006
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	Brazil: 71
Country: Number of subjects enrolled	Germany: 41
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Sweden: 9
Country: Number of subjects enrolled	United States: 156
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Saudi Arabia: 1
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Slovakia: 7
Country: Number of subjects enrolled	Czech Republic: 27
Country: Number of subjects enrolled	Greece: 9

Worldwide total number of subjects	334
EEA total number of subjects	106

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)	242
From 65 to 84 years	91
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

First subject, first visit was 17 May 2006 and last subject, last visit was 05 Dec 2013.

Pre-assignment

Screening details:

There was a screening period of up to 14 days to assess eligibility. A total of 377 patients were screened.

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
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Arm title	Bosentan
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Arm description: -

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

Dosage and administration details:

62.5 mg BID for 4 weeks followed by 125 mg BID maintenance dose

Arm title	Placebo
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Arm description: -

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

Dosage and administration details:

62.5 mg BID for 4 weeks followed by 125 mg BID maintenance dose

Number of subjects in period 1	Bosentan	Placebo
Started	159	175
Completed	76	86
Not completed	83	89
Adverse event, serious fatal	33	44
Decision by the investigator	5	7

Lung transplantation	1	1
Withdrawal of consent	32	26
Lost to follow-up	5	4
Administrative reason	7	7

Baseline characteristics

Reporting groups

Reporting group title	Bosentan
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Bosentan	Placebo	Total
Number of subjects	159	175	334
Age categorical Units: Subjects			

Age continuous			
Age continuous description			
Units: years			
arithmetic mean	52.9	54.7	
standard deviation	± 15.44	± 15.73	-
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	125	128	253
Male	34	47	81
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian/White	147	149	296
Black	7	12	19
Hispanic	5	6	11
Other	0	8	8
Region of Enrollment			
Units: Subjects			
Brazil	36	35	71
Czech Republic	12	15	27
Denmark	3	4	7
Germany	19	22	41
Greece	4	5	9
Portugal	3	0	3
Saudi Arabia	0	1	1
Slovakia	4	3	7
Spain	1	1	2
Sweden	4	5	9
United Kingdom	0	1	1
United States	73	83	156

End points

End points reporting groups

Reporting group title	Bosentan
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Time to first confirmed morbidity/mortality event up to the end of study

End point title	Time to first confirmed morbidity/mortality event up to the end of study
End point description:	Kaplan-Meier estimate of percentage of participants without a morbidity/mortality event. A morbidity/mortality event is defined as the occurrence of a) death, b) hospitalization for worsening or complication of PAH or intravenous prostanoid initiation, c) atrial septostomy, d) lung transplantation, or e) worsening PAH, defined as "moderately" or "markedly" worsened PAH symptoms using a patient global self-assessment (PGSA) scale AND initiation of inhaled or subcutaneous prostanoids or the disease progression package (open-label bosentan). If a patient replied "no change" or "mildly worse" on the PGSA, a decrease in 6MWT of 20% versus last visit or 30% versus baseline is also required to confirm the event.
End point type	Primary
End point timeframe:	From baseline to end of study, approximately 86 months

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	175		
Units: percentage of participants-Kaplan Meier				
number (not applicable)				
Kaplan-Meier estimate at Month 4	96.1	90.6		
Kaplan-Meier estimate at Month 8	90.5	83		
Kaplan-Meier estimate at Month 12	82.7	74		
Kaplan-Meier estimate at Month 16	74.7	71		
Kaplan-Meier estimate at Month 20	71.8	66.1		
Kaplan-Meier estimate at Month 24	66.6	61.5		
Kaplan-Meier estimate at Month 28	65.8	55		
Kaplan-Meier estimate at Month 32	62.4	52.7		
Kaplan-Meier estimate at Month 34	57.5	48.8		
Kaplan-Meier estimate at Month 40	56.4	48		
Kaplan-Meier estimate at Month 44	50.6	46.2		
Kaplan-Meier estimate at Month 48	46.7	45.2		
Kaplan-Meier estimate at Month 52	45.1	45.2		
Kaplan-Meier estimate at Month 56	45.1	42.6		
Kaplan-Meier estimate at Month 60	45.1	39.7		
Kaplan-Meier estimate at Month 64	45.1	39.7		
Kaplan-Meier estimate at Month 68	40.1	39.7		
Kaplan-Meier estimate at Month 72	40.1	39.7		

Kaplan-Meier estimate at Month 76	40.1	36.1		
Kaplan-Meier estimate at Month 80	40.1	36.1		
Kaplan-Meier estimate at Month 84	40.1	36.1		
Kaplan-Meier estimate at End of Study	40.1	36.1		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Bosentan v Placebo
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2508
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.831
Confidence interval	
level	Other: 97.31 %
sides	2-sided
lower limit	0.582
upper limit	1.187

Secondary: Time to first confirmed death, hospitalization for worsening or complication of PAH or initiation of intravenous prostanoids, atrial septostomy, or lung transplantation

End point title	Time to first confirmed death, hospitalization for worsening or complication of PAH or initiation of intravenous prostanoids, atrial septostomy, or lung transplantation
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End point description:

Kaplan-Meier estimate of percentage of participants without an event of death, hospitalization (for worsening or complication of PAH or initiation of intravenous prostanoids), atrial septostomy or lung transplantation. Time to first confirmed death, hospitalization (for worsening or complication of PAH or initiation of intravenous prostanoids), atrial septostomy or lung transplantation from baseline to end of study was confirmed by an independent Clinical Endpoint Committee.

End point type	Secondary
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End point timeframe:

Baseline to end of study, approximately 86 months

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	175		
Units: percentage of participants-Kaplan Meier				
number (not applicable)				
Kaplan-Meier estimate at Month 4	97.4	95.3		
Kaplan-Meier estimate at Month 8	94.6	91.8		

Kaplan-Meier estimate at Month 12	89.6	88.8		
Kaplan-Meier estimate at Month 16	85.3	86.9		
Kaplan-Meier estimate at Month 20	82.3	83.8		
Kaplan-Meier estimate at Month 24	76.9	79.8		
Kaplan-Meier estimate at Month 28	76.1	74.7		
Kaplan-Meier estimate at Month 32	75.2	73.1		
Kaplan-Meier estimate at Month 36	72.2	64.4		
Kaplan-Meier estimate at Month 40	72.2	61.9		
Kaplan-Meier estimate at Month 44	64.2	60.1		
Kaplan-Meier estimate at Month 48	60.3	58.1		
Kaplan-Meier estimate at Month 52	57.4	56.8		
Kaplan-Meier estimate at Month 56	53.8	52.7		
Kaplan-Meier estimate at Month 60	53.8	51.3		
Kaplan-Meier estimate at Month 64	53.8	51.3		
Kaplan-Meier estimate at Month 68	39.8	49.2		
Kaplan-Meier estimate at Month 72	39.8	49.2		
Kaplan-Meier estimate at Month 76	39.8	45.1		
Kaplan-Meier estimate at Month 80	39.8	45.1		
Kaplan-Meier estimate at Month 84	39.8	45.1		
Kaplan-Meier estimate at End of Study	39.8	45.1		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Bosentan v Placebo
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8385
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.963
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.673
upper limit	1.38

Secondary: Change from baseline to Week 16 in 6 minute walk test (6MWT)

End point title	Change from baseline to Week 16 in 6 minute walk test (6MWT)
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End point description:

The 6MWT is a non-encouraged test, which measures the distance covered over a 6 minute walk; the patient is instructed to walk as far as possible in a 30 m long flat corridor, back and forth around two cones, with the permission to slow down, rest, or stop if needed. Areas were to be well ventilated with air temperature controlled between 20 °C and 23 °C (68 °F to 76 °F). The test was to be administered at the same time of day and by the same tester throughout the study. The tester measured the distance walked by non-encouraged patients during the timed 6 minute period.

End point type	Secondary
End point timeframe:	
From baseline to week 16	

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	175		
Units: Meters				
arithmetic mean (standard deviation)				
Baseline	363 (± 78.5)	358 (± 73.1)		
Week 16	370 (± 98.3)	343 (± 107.3)		
Change from baseline	7.2 (± 66.01)	-14.6 (± 80.42)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Bosentan v Placebo
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0106
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)
Point estimate	21.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.9
upper limit	37.8

Secondary: Number of Participants With Improved, No Change, or Worsened World Health Organisation Functional Class From Baseline to Week 16

End point title	Number of Participants With Improved, No Change, or Worsened World Health Organisation Functional Class From Baseline to Week 16
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End point description:

Class I: no limitation of usual physical activity (PA) which does not increase dyspnea, fatigue, chest pain, or presyncope. Class II: mild limitation of PA. No discomfort at rest. Normal PA increases dyspnea, fatigue, chest pain, or presyncope. Class III: marked limitation of PA. No discomfort at rest. Less than ordinary activity increases dyspnea, fatigue, chest pain, or presyncope. Class IV: unable to perform any PA and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest and symptoms are increased by almost any PA.

End point type	Secondary
End point timeframe:	
From baseline to Week 16	

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	175		
Units: participants				
Improved	25	28		
No change	121	130		
Worsened	13	17		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Bosentan
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Fisher exact
Parameter estimate	Relative risk of improvement
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.61

Secondary: Time to death of all causes from baseline to end of study

End point title	Time to death of all causes from baseline to end of study
End point description:	Kaplan-Meier estimate of percentage of participants without a mortality event. Time to death due to any cause.
End point type	Secondary
End point timeframe:	Baseline to End of Study, approximately 86 months

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	175		
Units: percentage of participants-Kaplan Meier				
number (not applicable)				
Kaplan-Meier estimate at Month 4	99.4	98.2		
Kaplan-Meier estimate at Month 8	98.7	95.8		
Kaplan-Meier estimate at Month 12	96.5	94		
Kaplan-Meier estimate at Month 16	92.8	92.8		
Kaplan-Meier estimate at Month 20	90.6	89.5		
Kaplan-Meier estimate at Month 24	89.1	88.2		
Kaplan-Meier estimate at Month 28	85.8	85.9		
Kaplan-Meier estimate at Month 32	85.8	84.3		
Kaplan-Meier estimate at Month 36	85.8	78.5		
Kaplan-Meier estimate at Month 40	85.8	76.8		
Kaplan-Meier estimate at Month 44	81.4	74.9		
Kaplan-Meier estimate at Month 48	77.7	71.8		
Kaplan-Meier estimate at Month 52	75	70.5		
Kaplan-Meier estimate at Month 56	70.1	66.4		
Kaplan-Meier estimate at Month 60	67.8	64.9		
Kaplan-Meier estimate at Month 64	67.8	64.9		
Kaplan-Meier estimate at Month 68	67.8	64.9		
Kaplan-Meier estimate at Month 72	67.8	64.9		
Kaplan-Meier estimate at Month 76	67.8	60.3		
Kaplan-Meier estimate at Month 80	58.1	60.3		
Kaplan-Meier estimate at Month 84	58.1	60.3		
Kaplan-Meier estimate at End of Study	58.1	60.3		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Bosentan v Placebo
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4974
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.855
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.544
upper limit	1.344

Secondary: Adjusted Percentage Ratio from Baseline in N-terminal Pro-B-type

Natriuretic Peptide (NT-pro-BNP)

End point title	Adjusted Percentage Ratio from Baseline in N-terminal Pro-B-type Natriuretic Peptide (NT-pro-BNP)
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End point description:

Blood sampling for the measurement of NT-pro-BNP was performed and the plasma concentrations of NT-pro-BNP were determined by a certified centralized laboratory.

End point type	Secondary
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End point timeframe:

Baseline to Month 20

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	117		
Units: Adjusted percentage ratio from baseline				
geometric mean (confidence interval 95%)				
Month 1 to Baseline	87.46 (77.12 to 99.18)	110.02 (97.56 to 124.06)		
Month 4 to Baseline	92.65 (81.2 to 105.72)	113.2 (99.61 to 128.65)		
Month 8 to Baseline	85.21 (72.58 to 100.05)	122.87 (104.82 to 144.02)		
Month 12 to Baseline	84.48 (71.48 to 99.83)	132.11 (111.95 to 155.89)		
Month 16 to Baseline	92.69 (75.75 to 113.42)	129.92 (106.69 to 158.2)		
Month 20 to Baseline	98.36 (79.46 to 121.75)	143.17 (115.86 to 176.91)		
Treatment effect over 20 months	92.54 (82.72 to 103.52)	121 (108.42 to 135.05)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Bosentan
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0003
Method	Repeated measures analysis
Parameter estimate	Percentage change over placebo
Point estimate	-23.52

Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.69
upper limit	-11.79

Secondary: Change from baseline to Week 16 in Borg dyspnea index

End point title	Change from baseline to Week 16 in Borg dyspnea index
End point description:	
The Borg dyspnea index was evaluated immediately after the 6MWT to obtain a rating of dyspnea at the end of the exercise using a scale from 0 ('Nothing at all') to 10 ('Very, very severe – maximal').	
End point type	Secondary
End point timeframe:	
Baseline to Week 16	

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	175		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	3.5 (± 1.99)	3.7 (± 2.18)		
Week 16	3.4 (± 2.12)	3.6 (± 2.24)		
Change from baseline	-0.09 (± 1.693)	-0.08 (± 2.035)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Bosentan v Placebo
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9566
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	0.39

Secondary: Change from baseline to Week 16 in the EuroQol 5 Dimensions (EQ-5D) questionnaire calculated score

End point title	Change from baseline to Week 16 in the EuroQol 5 Dimensions (EQ-5D) questionnaire calculated score
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End point description:

The EQ-5D questionnaire is a patient-reported outcome consisting of a 5 dimensional descriptive system and a visual analog scale (VAS). The descriptive system asks respondents to describe their health status. Health is defined in 5 dimensions: (1) mobility, (2) self care, (3) usual activities, (4) pain or discomfort, and (5) anxiety or depression. Each dimension is divided into 3 levels, indicating (a) no problem, (b) some or moderate problems, or (c) extreme problems. Respondents record their problem(s) in each of the 5 dimensions. Combinations of these levels define a total of 243 health states. A health state defined by the descriptive system of EQ-5D can be described by a 5-digit number with full health is indicated by 11111 and poorest health state by 33333. The EQ-5D calculated score was derived by re-assigning local scores for answers to each question and combining these local scores into a global score with ranges from 0 (worst possible outcome) to 1 (best possible outcome).

End point type	Secondary
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End point timeframe:

From baseline to Week 16

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	175		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	0.678 (± 0.2172)	0.681 (± 0.2138)		
Week 16	0.662 (± 0.2807)	0.645 (± 0.3062)		
Change from Baseline	-0.0161 (± 0.25232)	-0.0361 (± 0.26671)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Bosentan v Placebo
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5571
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.036
upper limit	0.076

Secondary: Change from baseline to Week 16 in the EuroQol 5 Dimensions (EQ-5D) visual analogue scale score

End point title	Change from baseline to Week 16 in the EuroQol 5 Dimensions (EQ-5D) visual analogue scale score
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End point description:

The EQ-5D questionnaire is a patient-reported outcome consisting of a 5 dimensional descriptive system and a visual analog scale (VAS) together with brief demographic questions. EQ-5D VAS asks respondents to rate their perception of their overall health on a vertical visual analogue scale with 'best imaginable health state' set at 100 and 'worst imaginable health state' set at 0.

End point type	Secondary
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End point timeframe:

Baseline to Week 16

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	175		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	67 ($\pm$ 17.4)	64 ($\pm$ 17.5)		
Week 16	69 ($\pm$ 19.9)	66 ($\pm$ 19.9)		
Change from Baseline	2.1 ($\pm$ 18.83)	2 ($\pm$ 17.01)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Bosentan v Placebo
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4086
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	4

Secondary: Patient Global Self Assessment (PGSA) Status at Week 16

End point title	Patient Global Self Assessment (PGSA) Status at Week 16
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End point description:

The PGSA is a questionnaire that allows the patient to compare his/her PAH status in response to the question "How do you feel about your PAH today compared with your last visit?" asked by the investigator. Patients use a seven-point scale to respond: markedly better, moderately better, mildly better, no change, markedly worse, moderately worse, or mildly worse.

End point type	Secondary
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End point timeframe:

Week 16

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	162		
Units: participants				
Markedly better	24	13		
Moderately better	23	30		
Mildly better	32	36		
No change	50	59		
Mildly worse	16	15		
Moderately worse	3	5		
Markedly worse	2	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to End of Study and up to 1 day after discontinuation of study treatment, approximately 86 weeks

Adverse event reporting additional description:

All treated patients. Treatment emergent adverse events.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo

placebo: Matching bosentan placebo/b.i.d.

Reporting group title	Bosentan
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Reporting group description:

Bosentan

bosentan: bosentan/62.5 mg tablet/b.i.d. for 4 weeks

then

bosentan/125 mg tablet/b.i.d.

Serious adverse events	Placebo	Bosentan	
Total subjects affected by serious adverse events			
subjects affected / exposed	102 / 174 (58.62%)	73 / 159 (45.91%)	
number of deaths (all causes)	22	9	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ACOUSTIC NEUROMA			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHIAL CARCINOMA			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHIOLOALVEOLAR CARCINOMA			

subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CERVIX CARCINOMA			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIFFUSE LARGE B-CELL LYMPHOMA			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLAMMATORY CARCINOMA OF THE BREAST			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT MELANOMA IN SITU			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENINGIOMA BENIGN			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTATIC MALIGNANT MELANOMA			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
RECTAL CANCER			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UTERINE LEIOMYOMA			

subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EXTREMITY NECROSIS			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL ARTERY OCCLUSION			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATOMA			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSION			
subjects affected / exposed	2 / 174 (1.15%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SHOCK HAEMORRHAGIC			

subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Surgical and medical procedures			
CHEMOTHERAPY			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY BYPASS			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIURETIC THERAPY			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FINGER AMPUTATION			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INCISIONAL HERNIA REPAIR			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
KNEE ARTHROPLASTY			
subjects affected / exposed	2 / 174 (1.15%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIOTHERAPY			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN CYST EXCISION			

subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN NEOPLASM EXCISION			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THYMECTOMY			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
PREGNANCY			
subjects affected / exposed	3 / 174 (1.72%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ADVERSE DRUG REACTION			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASTHENIA			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHEST PAIN			
subjects affected / exposed	7 / 174 (4.02%)	5 / 159 (3.14%)	
occurrences causally related to treatment / all	0 / 7	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEATH			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

FATIGUE			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	1 / 174 (0.57%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERALISED OEDEMA			
subjects affected / exposed	3 / 174 (1.72%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MULTI-ORGAN FAILURE			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
OEDEMA PERIPHERAL			
subjects affected / exposed	2 / 174 (1.15%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUDDEN DEATH			
subjects affected / exposed	1 / 174 (0.57%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Immune system disorders			
DRUG HYPERSENSITIVITY			
subjects affected / exposed	1 / 174 (0.57%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERSENSITIVITY			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
DYSMENORRHOEA			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENORRHAGIA			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OVARIAN MASS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UTERINE HAEMORRHAGE			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UTERINE PROLAPSE			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VAGINAL HAEMORRHAGE			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ACUTE PULMONARY OEDEMA			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE RESPIRATORY FAILURE			

subjects affected / exposed	1 / 174 (0.57%)	4 / 159 (2.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
ASTHMA			
subjects affected / exposed	1 / 174 (0.57%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATELECTASIS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHIAL HAEMORRHAGE			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHIAL HYPERREACTIVITY			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	2 / 174 (1.15%)	4 / 159 (2.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 0	
CHRONIC RESPIRATORY FAILURE			
subjects affected / exposed	0 / 174 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSпноEA			
subjects affected / exposed	8 / 174 (4.60%)	5 / 159 (3.14%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
EPISTAXIS			

subjects affected / exposed	2 / 174 (1.15%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOPTYSIS			
subjects affected / exposed	0 / 174 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOXIA			
subjects affected / exposed	0 / 174 (0.00%)	3 / 159 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
OBLITERATIVE BRONCHIOLITIS			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORTHOPNOEA			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURISY			
subjects affected / exposed	1 / 174 (0.57%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX			
subjects affected / exposed	0 / 174 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY ARTERIAL HYPERTENSION			
subjects affected / exposed	28 / 174 (16.09%)	25 / 159 (15.72%)	
occurrences causally related to treatment / all	2 / 31	1 / 29	
deaths causally related to treatment / all	0 / 4	0 / 4	
PULMONARY EMBOLISM			

subjects affected / exposed	1 / 174 (0.57%)	3 / 159 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY OEDEMA			
subjects affected / exposed	1 / 174 (0.57%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
RESPIRATORY DISTRESS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY FAILURE			
subjects affected / exposed	3 / 174 (1.72%)	6 / 159 (3.77%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
BIPOLAR I DISORDER			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEPRESSION			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENTAL STATUS CHANGES			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUICIDAL IDEATION			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUICIDE ATTEMPT			

subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 174 (0.57%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 174 (0.57%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ELECTROCARDIOGRAM QT PROLONGED			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC ENZYME INCREASED			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIVER FUNCTION TEST ABNORMAL			
subjects affected / exposed	0 / 174 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASCULAR RESISTANCE PULMONARY INCREASED			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

WEIGHT DECREASED			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	2 / 174 (1.15%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL NECK FRACTURE			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FOOT FRACTURE			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FRACTURED SACRUM			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIP FRACTURE			
subjects affected / exposed	2 / 174 (1.15%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HUMERUS FRACTURE			
subjects affected / exposed	0 / 174 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
INCISIONAL HERNIA			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

LACERATION			
subjects affected / exposed	1 / 174 (0.57%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER LIMB FRACTURE			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PELVIC FRACTURE			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL COMPLICATION			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL HAEMATOMA			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RIB FRACTURE			
subjects affected / exposed	1 / 174 (0.57%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBDURAL HAEMATOMA			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOXICITY TO VARIOUS AGENTS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSFUSION-RELATED ACUTE LUNG INJURY			

subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE RIGHT VENTRICULAR FAILURE			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANGINA PECTORIS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			
subjects affected / exposed	3 / 174 (1.72%)	4 / 159 (2.52%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FLUTTER			
subjects affected / exposed	1 / 174 (0.57%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRADYARRHYTHMIA			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRADYCARDIA			

subjects affected / exposed	0 / 174 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			
subjects affected / exposed	3 / 174 (1.72%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
CARDIAC FAILURE			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	1 / 174 (0.57%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COR PULMONALE			
subjects affected / exposed	1 / 174 (0.57%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CORONARY ARTERY DISEASE			
subjects affected / exposed	1 / 174 (0.57%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTRACARDIAC THROMBUS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL INFARCTION			
subjects affected / exposed	2 / 174 (1.15%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
RIGHT VENTRICULAR FAILURE			

subjects affected / exposed	8 / 174 (4.60%)	6 / 159 (3.77%)	
occurrences causally related to treatment / all	0 / 9	1 / 6	
deaths causally related to treatment / all	0 / 3	0 / 1	
SICK SINUS SYNDROME			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	1 / 174 (0.57%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRIFASCICULAR BLOCK			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
BRAIN STEM STROKE			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	2 / 174 (1.15%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
CONVULSION			
subjects affected / exposed	2 / 174 (1.15%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIZZINESS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEADACHE			

subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEMIPARESIS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOAESTHESIA			
subjects affected / exposed	2 / 174 (1.15%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUMBAR RADICULOPATHY			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYASTHENIA GRAVIS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUROPATHY PERIPHERAL			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PRESYNCOPE			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SCIATICA			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			

subjects affected / exposed	6 / 174 (3.45%)	3 / 159 (1.89%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	3 / 174 (1.72%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	2 / 174 (1.15%)	3 / 159 (1.89%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAEMIA HAEMOLYTIC AUTOIMMUNE			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
HYPERSPLENISM			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPLENOMEGALY			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOTIC THROMBOCYTOPENIC PURPURA			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

SUDDEN HEARING LOSS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Eye disorders			
EYE SWELLING			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RETINAL DETACHMENT			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	3 / 174 (1.72%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 174 (0.57%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASCITES			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULUM			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

DYSPHAGIA			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL DISORDER			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 174 (0.57%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATEMESIS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATOCHYZIA			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINE POLYP			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESOPHAGEAL VARICES HAEMORRHAGE			

subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL HAEMORRHAGE			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 174 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 174 (0.57%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
BILIARY DYSKINESIA			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS ACUTE			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLESTASIS			

subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC CIRRHOSIS			
subjects affected / exposed	1 / 174 (0.57%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
PORTAL HYPERTENSION			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
SKIN ULCER			
subjects affected / exposed	1 / 174 (0.57%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URTICARIA			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
BLADDER NECK OBSTRUCTION			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATURIA			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEPHROLITHIASIS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			

subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE ACUTE			
subjects affected / exposed	4 / 174 (2.30%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL IMPAIRMENT			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL TUBULAR NECROSIS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACK PAIN			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLLAGEN DISORDER			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CREST SYNDROME			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
DUPUYTREN'S CONTRACTURE			

subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMARTHROSIS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEONECROSIS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN IN EXTREMITY			
subjects affected / exposed	2 / 174 (1.15%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ROTATOR CUFF SYNDROME			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYSTEMIC LUPUS ERYTHEMATOSUS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ABDOMINAL ABSCESS			

subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDICITIS			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACTERAEMIA			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
subjects affected / exposed	3 / 174 (1.72%)	6 / 159 (3.77%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS VIRAL			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHOPNEUMONIA			
subjects affected / exposed	1 / 174 (0.57%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CELLULITIS			
subjects affected / exposed	0 / 174 (0.00%)	3 / 159 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE COLITIS			
subjects affected / exposed	0 / 174 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE INFECTION			

subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DENGUE FEVER			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED SEPSIS			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULITIS			
subjects affected / exposed	0 / 174 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	5 / 174 (2.87%)	3 / 159 (1.89%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
GASTROENTERITIS CALICIVIRAL			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS SALMONELLA			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 INFLUENZA			

subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATOMA INFECTION			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTED DERMAL CYST			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTIVE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
KLEBSIELLA BACTERAEemia			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG INFECTION			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOCOCCAL SEPSIS			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			

subjects affected / exposed	6 / 174 (3.45%)	11 / 159 (6.92%)	
occurrences causally related to treatment / all	0 / 9	0 / 16	
deaths causally related to treatment / all	0 / 1	0 / 0	
PNEUMONIA STAPHYLOCOCCAL			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
POSTOPERATIVE WOUND INFECTION			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS			
subjects affected / exposed	1 / 174 (0.57%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
SEPSIS			
subjects affected / exposed	1 / 174 (0.57%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS SYNDROME			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPTIC SHOCK			
subjects affected / exposed	2 / 174 (1.15%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
SINUSITIS			

subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUBERCULOSIS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 174 (0.57%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 174 (1.15%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
UROSEPSIS			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 174 (1.15%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND INFECTION			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			

subjects affected / exposed	0 / 174 (0.00%)	3 / 159 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
FLUID OVERLOAD			
subjects affected / exposed	0 / 174 (0.00%)	3 / 159 (1.89%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
FLUID RETENTION			
subjects affected / exposed	1 / 174 (0.57%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GOUT			
subjects affected / exposed	1 / 174 (0.57%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERKALAEMIA			
subjects affected / exposed	0 / 174 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERVOLAEMIA			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOKALAEMIA			
subjects affected / exposed	0 / 174 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Bosentan	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	147 / 174 (84.48%)	135 / 159 (84.91%)	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	7 / 174 (4.02%)	16 / 159 (10.06%)	
occurrences (all)	9	21	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	8 / 174 (4.60%)	13 / 159 (8.18%)	
occurrences (all)	10	18	
LIVER FUNCTION TEST ABNORMAL			
subjects affected / exposed	4 / 174 (2.30%)	11 / 159 (6.92%)	
occurrences (all)	5	14	
HEPATIC ENZYME INCREASED			
subjects affected / exposed	3 / 174 (1.72%)	9 / 159 (5.66%)	
occurrences (all)	3	11	
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	6 / 174 (3.45%)	8 / 159 (5.03%)	
occurrences (all)	12	8	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	24 / 174 (13.79%)	24 / 159 (15.09%)	
occurrences (all)	29	26	
DIZZINESS			
subjects affected / exposed	17 / 174 (9.77%)	17 / 159 (10.69%)	
occurrences (all)	20	21	
General disorders and administration site conditions			
OEDEMA PERIPHERAL			
subjects affected / exposed	26 / 174 (14.94%)	30 / 159 (18.87%)	
occurrences (all)	29	37	
CHEST PAIN			
subjects affected / exposed	10 / 174 (5.75%)	18 / 159 (11.32%)	
occurrences (all)	12	26	
FATIGUE			

subjects affected / exposed occurrences (all)	19 / 174 (10.92%) 19	13 / 159 (8.18%) 15	
Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all)	10 / 174 (5.75%) 10	15 / 159 (9.43%) 21	
Gastrointestinal disorders DIARRHOEA subjects affected / exposed occurrences (all) NAUSEA subjects affected / exposed occurrences (all) ABDOMINAL PAIN subjects affected / exposed occurrences (all) VOMITING subjects affected / exposed occurrences (all)	19 / 174 (10.92%) 26 22 / 174 (12.64%) 28 12 / 174 (6.90%) 14 12 / 174 (6.90%) 13	19 / 159 (11.95%) 24 16 / 159 (10.06%) 22 11 / 159 (6.92%) 15 8 / 159 (5.03%) 10	
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all) DYSPNOEA subjects affected / exposed occurrences (all) PULMONARY ARTERIAL HYPERTENSION subjects affected / exposed occurrences (all) EPISTAXIS subjects affected / exposed occurrences (all) NASAL CONGESTION subjects affected / exposed occurrences (all)	21 / 174 (12.07%) 26 19 / 174 (10.92%) 21 35 / 174 (20.11%) 36 6 / 174 (3.45%) 6 0 / 174 (0.00%) 0	22 / 159 (13.84%) 28 21 / 159 (13.21%) 25 15 / 159 (9.43%) 16 12 / 159 (7.55%) 15 8 / 159 (5.03%) 9	
Skin and subcutaneous tissue disorders			

RASH subjects affected / exposed occurrences (all)	6 / 174 (3.45%) 8	10 / 159 (6.29%) 12	
Psychiatric disorders ANXIETY subjects affected / exposed occurrences (all)	11 / 174 (6.32%) 12	9 / 159 (5.66%) 11	
INSOMNIA subjects affected / exposed occurrences (all)	11 / 174 (6.32%) 11	8 / 159 (5.03%) 8	
Musculoskeletal and connective tissue disorders BACK PAIN subjects affected / exposed occurrences (all)	22 / 174 (12.64%) 27	15 / 159 (9.43%) 18	
ARTHRALGIA subjects affected / exposed occurrences (all)	20 / 174 (11.49%) 25	13 / 159 (8.18%) 17	
PAIN IN EXTREMITY subjects affected / exposed occurrences (all)	15 / 174 (8.62%) 16	9 / 159 (5.66%) 13	
MUSCLE SPASMS subjects affected / exposed occurrences (all)	6 / 174 (3.45%) 6	8 / 159 (5.03%) 8	
Infections and infestations UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all)	29 / 174 (16.67%) 44	21 / 159 (13.21%) 38	
URINARY TRACT INFECTION subjects affected / exposed occurrences (all)	13 / 174 (7.47%) 17	16 / 159 (10.06%) 34	
BRONCHITIS subjects affected / exposed occurrences (all)	18 / 174 (10.34%) 32	14 / 159 (8.81%) 24	
NASOPHARYNGITIS subjects affected / exposed occurrences (all)	15 / 174 (8.62%) 24	11 / 159 (6.92%) 15	

SINUSITIS			
subjects affected / exposed	12 / 174 (6.90%)	11 / 159 (6.92%)	
occurrences (all)	20	21	
PNEUMONIA			
subjects affected / exposed	8 / 174 (4.60%)	8 / 159 (5.03%)	
occurrences (all)	8	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported