Clinical trial results:
A multicenter, double-blind, placebo-controlled Phase 3 study assessing the safety and efficacy of selexipag on morbidity and mortality in patients with pulmonary arterial hypertension

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2009-014490-41
Trial protocol	BE DK FR ES SE CZ GB IE HU AT SK DE GR NL IT
Global end of trial date	27 April 2014

Results information

Result version number	v1 (current)
This version publication date	31 March 2016
First version publication date	31 March 2016

Trial information

Trial identification

Sponsor protocol code	AC-065A302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01106014
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, 4123
Public contact	clinical trial disclosure desk, Actelion Pharmaceuticals Ltd, clinical-trials-disclosure@actelion.com
Scientific contact	clinical trial disclosure desk, Actelion Pharmaceuticals Ltd, clinical-trials-disclosure@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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 April 2014
Global end of trial reached?	Yes
Global end of trial date	27 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the effect of selexipag (ACT-293987) on time to first morbidity and mortality (MM) event in patients with 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, and with the ethical principles laid down in the Declaration of Helsinki

Background therapy:

Background PAH therapies ongoing at the time of study entry, except for prostacyclin and prostacyclin analogs, were allowed if patients had been on a stable dose for at least 3 months prior to randomization.

Evidence for comparator: -

Actual start date of recruitment	30 December 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 24
Country: Number of subjects enrolled	Australia: 62
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belarus: 51
Country: Number of subjects enrolled	Belgium: 22
Country: Number of subjects enrolled	Canada: 38
Country: Number of subjects enrolled	Chile: 38
Country: Number of subjects enrolled	China: 140
Country: Number of subjects enrolled	Colombia: 3
Country: Number of subjects enrolled	Czech Republic: 23
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	France: 47
Country: Number of subjects enrolled	Germany: 61
Country: Number of subjects enrolled	Greece: 9
Country: Number of subjects enrolled	Hungary: 23
Country: Number of subjects enrolled	India: 23
Country: Number of subjects enrolled	Ireland: 6
Country: Number of subjects enrolled	Israel: 32
Country: Number of subjects enrolled	Italy: 8

Country: Number of subjects enrolled	Korea, Republic of: 31
Country: Number of subjects enrolled	Malaysia: 4
Country: Number of subjects enrolled	Mexico: 30
Country: Number of subjects enrolled	Netherlands: 13
Country: Number of subjects enrolled	Peru: 15
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Romania: 11
Country: Number of subjects enrolled	Russian Federation: 91
Country: Number of subjects enrolled	Serbia: 11
Country: Number of subjects enrolled	Singapore: 10
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Sweden: 15
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Taiwan: 12
Country: Number of subjects enrolled	Thailand: 8
Country: Number of subjects enrolled	Turkey: 22
Country: Number of subjects enrolled	Ukraine: 50
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	United States: 155
Worldwide total number of subjects	1156
EEA total number of subjects	302

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)	949
From 65 to 84 years	207
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 1351 patients were screened from 181 sites in 39 countries worldwide. Of these, 1156 were randomized.

Pre-assignment

Screening details:

Screening assessments were performed up to a maximum of 28 days before baseline

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

Blinding implementation details:

The sponsor and all people involved in the study were blinded to the treatment, except for the members of the Data Monitoring Committee (regular review of unblinded efficacy, safety and tolerability data), clinical trial supply manager and people in charge of the pharmacokinetic analyses.

Arms

Are arms mutually exclusive?	Yes
Arm title	Selexipag

Arm description:

During the 12-week titration phase, treatment was initiated at 200 µg twice daily (b.i.d.) and up-titrated weekly in 200 µg b.i.d. increments to the maximum tolerated dose (MTD) for each individual patient but not above 1600 µg b.i.d. At Week 12, patients continued the treatment at their individual MTD up to Week 26. Thereafter the dose could be up-titrated at scheduled visits if needed for patients receiving a dose < 1600 µg b.i.d. The dose could be decreased at any time in case of tolerability issues.

Arm type	Experimental
Investigational medicinal product name	selexipag
Investigational medicinal product code	ACT293987
Other name	NS304
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Each tablet contained 200 µg of selexipag

Arm title	Placebo

Arm description:

Matching placebo was administered following the same administration schedule as described for selexipag.

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablet had the same aspects as selexipag tablet

Number of subjects in period 1	Selexipag	Placebo
Started	574	582
Completed	289	252
Not completed	285	330
Consent withdrawn by subject	43	37
Adverse Event	78	42
Administrative	7	6
Morbidity or Mortality Primary Endpoint	155	242
Lost to follow-up	2	3

Baseline characteristics

Reporting groups	
Reporting group title	Selexipag
Reporting group description:	
During the 12-week titration phase, treatment was initiated at 200 µg twice daily (b.i.d.) and up-titrated weekly in 200 µg b.i.d. increments to the maximum tolerated dose (MTD) for each individual patient but not above 1600 µg b.i.d. At Week 12, patients continued the treatment at their individual MTD up to Week 26. Thereafter the dose could be up-titrated at scheduled visits if needed for patients receiving a dose < 1600 µg b.i.d. The dose could be decreased at any time in case of tolerability issues.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo was administered following the same administration schedule as described for selexipag.	

Reporting group values	Selexipag	Placebo	Total
Number of subjects	574	582	1156
Age categorical Units: Subjects			
18-64 years old	475	474	949
65-84 years old	99	108	207
Age continuous Units: years			
arithmetic mean	48.2	47.9	
standard deviation	± 15.19	± 15.55	-
Gender categorical Units:			
Female	457	466	923
Male	117	116	233
Ethnicity			
Number of patients in each ethnic group			
Units: Subjects			
Caucasian/white	376	375	751
Asian	125	120	245
Hispanic	51	63	114
Black	13	14	27
Other	9	10	19
PAH etiology			
Number of patients in each PAH etiology category			
Units: Subjects			
Idiopathic	312	337	649
Heritable	13	13	26
Associated with connective tissue disease	167	167	334
Assoc. with corrected (>= 12 Mo) congenital shunts	60	50	110
Associated with drug or toxin exposure	17	10	27
Associated with HIV infection	5	5	10
Modified NYHA/WHO Functional class			

(FC)			
Number of patients in each NYHA/WHO Functional class (FC) at screening. The WHO FC ranges from I to IV, with higher ranges indicating more severe functional restrictions.			
Units: Subjects			
FC I	4	5	9
FC II	274	255	529
FC III	293	314	607
FC IV	3	8	11
PAH medications at baseline			
Number of patients receiving PAH background medication at the time of study drug start.			
Units: Subjects			
None	112	124	236
Endothelin Receptor Agonists (ERA)	94	76	170
Phosphodiesterase type 5 inhibitors (PDE5I)	189	185	374
ERA and PDE5I in combination	179	197	376
Time since PAH diagnosis			
Units: Years			
median	0.9	1.1	
full range (min-max)	0 to 37.3	0 to 38.9	-
6-Minute walk distance (6MWD) at baseline			
Units: Meters			
median	376	369	
full range (min-max)	90 to 482	50 to 515	-

End points

End points reporting groups

Reporting group title	Selexipag

Reporting group description:

During the 12-week titration phase, treatment was initiated at 200 µg twice daily (b.i.d.) and up-titrated weekly in 200 µg b.i.d. increments to the maximum tolerated dose (MTD) for each individual patient but not above 1600 µg b.i.d. At Week 12, patients continued the treatment at their individual MTD up to Week 26. Thereafter the dose could be up-titrated at scheduled visits if needed for patients receiving a dose < 1600 µg b.i.d. The dose could be decreased at any time in case of tolerability issues.

Reporting group title	Placebo

Reporting group description:

Matching placebo was administered following the same administration schedule as described for selexipag.

Subject analysis set title	Full-analysis set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The full analysis set includes all randomized patients evaluated according to the study drug to which they have been randomized

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety analysis set includes all randomized patients who received at least one dose of study drug and were evaluated according to the study drug they have received

Primary: Time from randomization to the first morbidity event or death (all causes) up to 7 days after the last study drug intake

End point title	Time from randomization to the first morbidity event or death (all causes) up to 7 days after the last study drug intake

End point description:

Time from randomization to the first occurrence of a morbidity event or death (all causes) was analyzed with the Kaplan-Meier (KM) method (event-free KM estimates at different time points). Morbidity event was defined as any of the following events confirmed by the Critical Event Committee:
-Hospitalization for pulmonary arterial hypertension (PAH) worsening,
-Worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy,
-Initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH,
-Disease progression which was defined by a decrease in 6-minute walk distance from baseline (>=15%, confirmed by a 2nd test on a different day) combined with worsening of WHO FC for patients belonging to WHO FC II/III at baseline, or combined with the need for additional PAH specific therapy for patients belonging to WHO FC III/IV at baseline.
Note: The number of patients at risk decreased over time but this cannot be captured below

End point type	Primary

End point timeframe:

Up to 7 days after end of double-blind treatment (maximum: 4.3 years)

End point values	Selexipag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	574[1]	582[2]		
Units: Percentage of patients free of events				
number (confidence interval 95%)				
KM estimate at Month 6	91.2 (88.5 to 93.4)	81.7 (78.2 to 84.7)		

KM estimate at Month 12	83.1 (79.5 to 86.1)	70.6 (66.6 to 74.3)		
KM estimate at Month 18	75.5 (71.2 to 79.2)	61.3 (56.8 to 65.5)		
KM estimate at Month 24	67.9 (63 to 72.4)	53.9 (49 to 58.5)		
KM estimate at Month 30	61.9 (56.3 to 66.9)	49.3 (44.2 to 54.3)		
KM estimate at Month 36	58.2 (51.7 to 64.1)	41.7 (35.2 to 48)		

Notes:

[1] - This is the total number of subjects at start date, not the number at risk at each timepoint

[2] - This is the total number of subjects at start date, not the number at risk at each timepoint

Statistical analyses

Statistical analysis title	Logrank test and proportional hazard ratio

Statistical analysis description:

The primary analysis was performed on the Full Analysis Set by a one-sided unstratified log-rank test

Comparison groups	Placebo v Selexipag
Number of subjects included in analysis	1156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.46
upper limit	0.78

Notes:

[3] - one-sided pvalue

Secondary: Change from baseline to Week 26 in 6-minute Walk distance (6MWD) at trough

End point title	Change from baseline to Week 26 in 6-minute Walk distance (6MWD) at trough

End point description:

The 6-minute walk distance test (6MWD) is a non-encouraged test performed in a 30 m long flat corridor, where the patient is instructed to walk as far as possible, back and forth around two cones, with the permission to slow down, rest, or stop if needed. If the patient was used to taking bronchodilators before a walk, he/she was given them 5 to 30 min before the test. Also if the patient was on chronic oxygen therapy, oxygen was given at their standard rate during the test. Absolute change from baseline to Week 26 in 6MWD was measured at trough, i.e., either on the next day after the last study drug administration or at least 12 hours after study drug administration if on the same day.

End point type	Secondary

End point timeframe:

Week 26

End point values	Selexipag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	574	582		
Units: Meters				
median (full range (min-max))				
6MWD at baseline - Overall	376 (90 to 482)	369 (50 to 515)		
6MWD at Week 26 - Overall	370 (0 to 617)	346 (0 to 650)		
6MWD Change from baseline at Week 26	4 (-448 to 260)	-9 (-438 to 262)		

Statistical analyses

Statistical analysis title	Non-parametric ANCOVA

Statistical analysis description:

Non-parametric ANCOVA with 6MWD as covariate at baseline.
Missing values were imputed based on the following imputation rules: 1) if patient was unable to walk at week 26, 0 meter was imputed, 2) if rule 1 did not apply, the second lowest observed 6MWD value (10 meters) at Week 26 was imputed. Missing values were imputed for 21.6% of the subjects.

Comparison groups	Selexipag v Placebo
Number of subjects included in analysis	1156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0027 [4]
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	12
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	1
upper limit	24

Notes:

[4] - One-sided pvalue of the nonparametric ANCOVA, adjusted for 6minute walk distance at baseline

Secondary: Absence of worsening from baseline to Week 26 in modified NYHA/WHO functional class (WHO FC)

End point title	Absence of worsening from baseline to Week 26 in modified NYHA/WHO functional class (WHO FC)

End point description:

Patients with WHO FC IV at baseline were excluded from this analysis as they could not shift to a worse category

End point type	Secondary

End point timeframe:

Week 26

End point values	Selexipag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	571	574		
Units: Percentage of patients				
number (not applicable)	77.8	74.9		

Statistical analyses

Statistical analysis title	Cochran Mantel Haenszel test

Statistical analysis description:

Cochran-Mantel-Haenszel test stratified by WHO FC at baseline.
For patients with missing modified NYHA/WHO FC at Week 26, the modified NYHA/WHO FC is considered as having worsened from baseline at Week 26. Missing values were imputed for 18.3% of the subjects.

Comparison groups	Selexipag v Placebo
Number of subjects included in analysis	1145
Analysis specification	Pre-specified
Analysis type	equivalence[5]
P-value	= 0.2843 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.161
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.811
upper limit	1.664

Notes:

[5] - It was assumed that the probabilities for absence of worsening in WHO FC at Week 26 were the same for both treatment groups
[6] - Two-sided p-value

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline up to up to 7 days after end of treatment (EOT)

Adverse event reporting additional description:

Median duration of exposure to study drug was 70.7 weeks (range: 0.3–216.7 weeks) in the selexipag group and 63.7 weeks (range: 0.7–192.0 weeks) in the placebo group.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

This group includes patients who received at least one dose of placebo. Four patients who were randomized to placebo never received the drugs and another patient received selexipag by mistake (see Selexipag group for more details). Therefore, these patients were excluded from the placebo group in the safety analysis set.

Reporting group title	Selexipag

Reporting group description:

This group includes patients who received at least one dose of selexipag. One subject who was randomized to placebo received a single dose of 8 tablets of selexipag due to an error in the dispensation of the medication bottle. Therefore, this patient was assigned to the selexipag group in the safety analysis set.

Serious adverse events	Placebo	Selexipag	
Total subjects affected by serious adverse events			
subjects affected / exposed	272 / 577 (47.14%)	252 / 575 (43.83%)	
number of deaths (all causes)	41	49	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
BREAST CANCER			
subjects affected / exposed	3 / 577 (0.52%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BREAST CANCER RECURRENT			

subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL HAEMANGIOMA			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLORECTAL CANCER METASTATIC			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
DIFFUSE LARGE B-CELL LYMPHOMA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
HEPATIC NEOPLASM			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG ADENOCARCINOMA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHANGIOSIS CARCINOMATOSA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT MELANOMA			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
CIRCULATORY COLLAPSE			

subjects affected / exposed	1 / 577 (0.17%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEEP VEIN THROMBOSIS			
subjects affected / exposed	1 / 577 (0.17%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
EXTREMITY NECROSIS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FLUSHING			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATOMA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMODYNAMIC INSTABILITY			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
HYPERTENSION			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
subjects affected / exposed	3 / 577 (0.52%)	3 / 575 (0.52%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
HYPOVOLAEMIC SHOCK			

subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	1 / 577 (0.17%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL ARTERY THROMBOSIS			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHLEBITIS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOPHLEBITIS SUPERFICIAL			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASCULITIS			
subjects affected / exposed	0 / 577 (0.00%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENA CAVA THROMBOSIS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENOUS INSUFFICIENCY			

subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENOUS THROMBOSIS LIMB			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
BARIATRIC GASTRIC BALLOON INSERTION			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLADDER NECK SUSPENSION			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC PACEMAKER INSERTION			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIOVERSION			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CERVICAL CONISATION			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTECTOMY			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DRUG THERAPY CHANGED			

subjects affected / exposed	1 / 577 (0.17%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GLAUCOMA SURGERY			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMODIALYSIS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG TRANSPLANT			
subjects affected / exposed	1 / 577 (0.17%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
MASTECTOMY			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NASAL SEPTAL OPERATION			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SALPINGECTOMY			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (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	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
STEM CELL TRANSPLANT			

subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
TURBINECTOMY			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URETHRAL OPERATION			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
PREGNANCY			
subjects affected / exposed	1 / 577 (0.17%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RUPTURED ECTOPIC PREGNANCY			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 577 (0.00%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHEST DISCOMFORT			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHEST PAIN			
subjects affected / exposed	6 / 577 (1.04%)	6 / 575 (1.04%)	
occurrences causally related to treatment / all	0 / 8	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

DEATH			
subjects affected / exposed	2 / 577 (0.35%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
EXERCISE TOLERANCE DECREASED			
subjects affected / exposed	1 / 577 (0.17%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FATIGUE			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (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 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IMPAIRED HEALING			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MULTI-ORGAN FAILURE			
subjects affected / exposed	2 / 577 (0.35%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OEDEMA PERIPHERAL			

subjects affected / exposed	4 / 577 (0.69%)	3 / 575 (0.52%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUDDEN CARDIAC DEATH			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
SUDDEN DEATH			
subjects affected / exposed	4 / 577 (0.69%)	5 / 575 (0.87%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 4	0 / 5	
Immune system disorders			
HYPERSENSITIVITY			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG TRANSPLANT REJECTION			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
SARCOIDOSIS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SECONDARY IMMUNODEFICIENCY			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

CERVICAL DYSPLASIA			
subjects affected / exposed	0 / 577 (0.00%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYSTOCELE			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENDOMETRIOSIS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENORRHAGIA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OVARIAN CYST			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OVARIAN CYST RUPTURED			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (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 LUNG INJURY			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

ASTHMA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
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	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	13 / 577 (2.25%)	17 / 575 (2.96%)	
occurrences causally related to treatment / all	2 / 17	0 / 21	
deaths causally related to treatment / all	0 / 1	0 / 1	
DYSPNOEA EXERTIONAL			
subjects affected / exposed	2 / 577 (0.35%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPISTAXIS			
subjects affected / exposed	4 / 577 (0.69%)	4 / 575 (0.70%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOPTYSIS			
subjects affected / exposed	5 / 577 (0.87%)	5 / 575 (0.87%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
HYPOXIA			
subjects affected / exposed	3 / 577 (0.52%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
ORGANISING PNEUMONIA			

subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORTHOPNOEA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY ARTERIAL HYPERTENSION			
subjects affected / exposed	127 / 577 (22.01%)	83 / 575 (14.43%)	
occurrences causally related to treatment / all	2 / 183	2 / 106	
deaths causally related to treatment / all	1 / 16	0 / 19	
PULMONARY ARTERY DILATATION			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	3 / 577 (0.52%)	4 / 575 (0.70%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY HAEMORRHAGE			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY HYPERTENSION			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY INFARCTION			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY OEDEMA			

subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY VENO-OCCLUSIVE DISEASE			
subjects affected / exposed	1 / 577 (0.17%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY FAILURE			
subjects affected / exposed	3 / 577 (0.52%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
RESPIRATORY GAS EXCHANGE DISORDER			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SLEEP APNOEA SYNDROME			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TACHYPNOEA			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
ALCOHOLISM			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENTAL STATUS CHANGES			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SCHIZOAFFECTIVE DISORDER			

subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SOMNAMBULISM			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STRESS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUICIDE ATTEMPT			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 577 (0.17%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRAIN NATRIURETIC PEPTIDE INCREASED			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC INDEX DECREASED			
subjects affected / exposed	1 / 577 (0.17%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

CATHETERISATION CARDIAC			
subjects affected / exposed	1 / 577 (0.17%)	3 / 575 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERNATIONAL NORMALISED RATIO INCREASED			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INVESTIGATION			
subjects affected / exposed	1 / 577 (0.17%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIVER FUNCTION TEST ABNORMAL			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OXYGEN SATURATION DECREASED			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY ARTERIAL PRESSURE INCREASED			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY ARTERIAL WEDGE PRESSURE INCREASED			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RED BLOOD CELL COUNT INCREASED			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

TRANSPLANT EVALUATION			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WALKING DISTANCE TEST ABNORMAL			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WEIGHT DECREASED			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WEIGHT INCREASED			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (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			
ACCIDENT			
subjects affected / exposed	1 / 577 (0.17%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACETABULUM FRACTURE			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRAIN HERNIATION			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CRANIOCEREBRAL INJURY			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

FALL			
subjects affected / exposed	6 / 577 (1.04%)	3 / 575 (0.52%)	
occurrences causally related to treatment / all	0 / 8	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL NECK FRACTURE			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMUR FRACTURE			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FOOT FRACTURE			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GINGIVAL INJURY			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEAD INJURY			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INJURY			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
JAW FRACTURE			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
JOINT DISLOCATION			

subjects affected / exposed	1 / 577 (0.17%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIGAMENT SPRAIN			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIP INJURY			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER LIMB FRACTURE			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUMBAR VERTEBRAL FRACTURE			
subjects affected / exposed	2 / 577 (0.35%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MULTIPLE INJURIES			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
PELVIC FRACTURE			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (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 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL HAEMATOMA			

subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL HAEMORRHAGE			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROCEDURAL HAEMORRHAGE			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PUBIS FRACTURE			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY FUME INHALATION DISORDER			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ROAD TRAFFIC ACCIDENT			
subjects affected / exposed	2 / 577 (0.35%)	4 / 575 (0.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 2	
SUBDURAL HAEMATOMA			
subjects affected / exposed	0 / 577 (0.00%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
TOXICITY TO VARIOUS AGENTS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRAUMATIC FRACTURE			

subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VACCINATION COMPLICATION			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASCULAR PROCEDURE COMPLICATION			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASCULAR PSEUDOANEURYSM			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
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 / 577 (0.17%)	0 / 575 (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 / 577 (0.00%)	1 / 575 (0.17%)	
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	5 / 577 (0.87%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
ANGINA PECTORIS			
subjects affected / exposed	1 / 577 (0.17%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARRHYTHMIA			

subjects affected / exposed	1 / 577 (0.17%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			
subjects affected / exposed	4 / 577 (0.69%)	7 / 575 (1.22%)	
occurrences causally related to treatment / all	0 / 5	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FLUTTER			
subjects affected / exposed	5 / 577 (0.87%)	3 / 575 (0.52%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL TACHYCARDIA			
subjects affected / exposed	2 / 577 (0.35%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL THROMBOSIS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIOVENTRICULAR BLOCK SECOND DEGREE			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRADYARRHYTHMIA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRADYCARDIA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CARDIAC ARREST			

subjects affected / exposed	4 / 577 (0.69%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
CARDIAC FAILURE			
subjects affected / exposed	2 / 577 (0.35%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	1 / 577 (0.17%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIO-RESPIRATORY ARREST			
subjects affected / exposed	2 / 577 (0.35%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
CARDIOGENIC SHOCK			
subjects affected / exposed	2 / 577 (0.35%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
CARDIOPULMONARY FAILURE			
subjects affected / exposed	1 / 577 (0.17%)	3 / 575 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
CHRONIC RIGHT VENTRICULAR FAILURE			
subjects affected / exposed	2 / 577 (0.35%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
COR PULMONALE			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COR PULMONALE ACUTE			

subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COR PULMONALE CHRONIC			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY INSUFFICIENCY			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CORONARY ARTERY OCCLUSION			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CORONARY ARTERY STENOSIS			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYANOSIS			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (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	1 / 577 (0.17%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
PALPITATIONS			
subjects affected / exposed	1 / 577 (0.17%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
RIGHT VENTRICULAR DYSFUNCTION			

subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RIGHT VENTRICULAR FAILURE			
subjects affected / exposed	41 / 577 (7.11%)	34 / 575 (5.91%)	
occurrences causally related to treatment / all	1 / 49	1 / 42	
deaths causally related to treatment / all	1 / 6	0 / 7	
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	4 / 577 (0.69%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TACHYCARDIA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENTRICULAR FIBRILLATION			
subjects affected / exposed	0 / 577 (0.00%)	3 / 575 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
VENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
AGEUSIA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
APHASIA			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATAXIA			

subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
AUTONOMIC NERVOUS SYSTEM IMBALANCE			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBELLAR SYNDROME			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL INFARCTION			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEMYELINATION			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIZZINESS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
HEADACHE			

subjects affected / exposed	0 / 577 (0.00%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOGLYCAEMIC UNCONSCIOUSNESS			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ISCHAEMIC STROKE			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOSS OF CONSCIOUSNESS			
subjects affected / exposed	1 / 577 (0.17%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENTAL IMPAIRMENT			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MIGRAINE			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARKINSON'S DISEASE			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST HERPETIC NEURALGIA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
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 / 577 (0.17%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBARACHNOID HAEMORRHAGE			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	20 / 577 (3.47%)	10 / 575 (1.74%)	
occurrences causally related to treatment / all	3 / 23	4 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
THALAMIC INFARCTION			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	0 / 577 (0.00%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOCAL CORD PARALYSIS			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	3 / 577 (0.52%)	5 / 575 (0.87%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGIC ANAEMIA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IDIOPATHIC THROMBOCYTOPENIC PURPURA			

subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEUKOPENIA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
CATARACT			
subjects affected / exposed	0 / 577 (0.00%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOROIDITIS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MACULOPATHY			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VISION BLURRED			

subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL DISCOMFORT			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL DISTENSION			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL HERNIA			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN			
subjects affected / exposed	4 / 577 (0.69%)	5 / 575 (0.87%)	
occurrences causally related to treatment / all	1 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAL HAEMORRHAGE			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASCITES			
subjects affected / exposed	0 / 577 (0.00%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS ISCHAEMIC			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
DIARRHOEA			

subjects affected / exposed	3 / 577 (0.52%)	3 / 575 (0.52%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
DUODENAL ULCER			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPEPSIA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTERITIS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROCELE			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS			
subjects affected / exposed	1 / 577 (0.17%)	3 / 575 (0.52%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL ANGIODYSPLASIA HAEMORRHAGIC			
subjects affected / exposed	1 / 577 (0.17%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	3 / 577 (0.52%)	3 / 575 (0.52%)	
occurrences causally related to treatment / all	2 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROOESOPHAGEAL REFLUX DISEASE			

subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATEMESIS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATOCHEZIA			
subjects affected / exposed	2 / 577 (0.35%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ILEUS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINE POLYP			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MELAENA			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NECROTISING COLITIS			

subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
OESOPHAGEAL OBSTRUCTION			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGEAL VARICES HAEMORRHAGE			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS ACUTE			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SIGMOIDITIS			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 577 (0.17%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	2 / 577 (0.35%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			

ACUTE HEPATIC FAILURE			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLANGITIS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS ACUTE			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLELITHIASIS			
subjects affected / exposed	2 / 577 (0.35%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC CIRRHOSIS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC CYST			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC MASS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATORENAL SYNDROME			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NODULAR REGENERATIVE HYPERPLASIA			

subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
DERMATITIS CONTACT			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DERMATOMYOSITIS			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN OF SKIN			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SCLERODERMA ASSOCIATED DIGITAL ULCER			
subjects affected / exposed	1 / 577 (0.17%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN ULCER			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TELANGIECTASIA			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (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			

ACUTE PRERENAL FAILURE			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANURIA			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUPUS NEPHRITIS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OLIGURIA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
subjects affected / exposed	1 / 577 (0.17%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE ACUTE			
subjects affected / exposed	6 / 577 (1.04%)	6 / 575 (1.04%)	
occurrences causally related to treatment / all	1 / 6	0 / 6	
deaths causally related to treatment / all	1 / 3	0 / 2	
URETHRAL STENOSIS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
AUTOIMMUNE THYROIDITIS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BASEDOW'S DISEASE			

subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTHYROIDISM			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTHYROIDISM			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	0 / 577 (0.00%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHONDROCALCINOSIS PYROPHOSPHATE			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (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 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CRYSTAL ARTHROPATHY			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (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 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

MIXED CONNECTIVE TISSUE DISEASE			
subjects affected / exposed	0 / 577 (0.00%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYALGIA			
subjects affected / exposed	0 / 577 (0.00%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOPOROSIS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOPOROTIC FRACTURE			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 577 (0.00%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
POLYMYOSITIS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RHEUMATOID ARTHRITIS			
subjects affected / exposed	2 / 577 (0.35%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STILL'S DISEASE ADULT ONSET			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYSTEMIC LUPUS ERYTHEMATOSUS			

subjects affected / exposed	1 / 577 (0.17%)	5 / 575 (0.87%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYSTEMIC SCLEROSIS			
subjects affected / exposed	2 / 577 (0.35%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
ABDOMINAL INFECTION			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABSCESS INTESTINAL			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABSCESS LIMB			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABSCESS ORAL			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDICITIS PERFORATED			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATYPICAL PNEUMONIA			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			

subjects affected / exposed	4 / 577 (0.69%)	6 / 575 (1.04%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHOPNEUMONIA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CATHETER SITE INFECTION			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	3 / 577 (0.52%)	3 / 575 (0.52%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE COLITIS			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYSTITIS ESCHERICHIA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETIC GANGRENE			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
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 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROCOLITIS VIRAL			

subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			
subjects affected / exposed	0 / 577 (0.00%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	3 / 577 (0.52%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATITIS C			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
subjects affected / exposed	0 / 577 (0.00%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOBAR PNEUMONIA			
subjects affected / exposed	2 / 577 (0.35%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOCALISED INFECTION			

subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	4 / 577 (0.69%)	4 / 575 (0.70%)	
occurrences causally related to treatment / all	1 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG ABSCESS			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
LUNG INFECTION			
subjects affected / exposed	2 / 577 (0.35%)	4 / 575 (0.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHANGITIS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NASOPHARYNGITIS			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOMYELITIS			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARAINFLUENZAE VIRUS INFECTION			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAROTITIS			

subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERITONITIS			
subjects affected / exposed	2 / 577 (0.35%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PILONIDAL CYST			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	25 / 577 (4.33%)	17 / 575 (2.96%)	
occurrences causally related to treatment / all	0 / 30	0 / 18	
deaths causally related to treatment / all	0 / 2	0 / 2	
PNEUMONIA BACTERIAL			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL INFECTION			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL SEPSIS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
PYELONEPHRITIS			
subjects affected / exposed	1 / 577 (0.17%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS ACUTE			

subjects affected / exposed	0 / 577 (0.00%)	3 / 575 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS CHRONIC			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	3 / 577 (0.52%)	4 / 575 (0.70%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	1 / 577 (0.17%)	3 / 575 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
SEPTIC SHOCK			
subjects affected / exposed	1 / 577 (0.17%)	3 / 575 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
STAPHYLOCOCCAL SEPSIS			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOOTH ABSCESS			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOOTH INFECTION			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRACHEOBRONCHITIS			

subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	3 / 577 (0.52%)	4 / 575 (0.70%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 577 (0.17%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL INFECTION			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	2 / 577 (0.35%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
DIABETES MELLITUS INADEQUATE CONTROL			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSLIPIDAEMIA			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ELECTROLYTE IMBALANCE			
subjects affected / exposed	1 / 577 (0.17%)	2 / 575 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
FLUID OVERLOAD			

subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FLUID RETENTION			
subjects affected / exposed	1 / 577 (0.17%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GOUT			
subjects affected / exposed	1 / 577 (0.17%)	0 / 575 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOGLYCAEMIA			
subjects affected / exposed	1 / 577 (0.17%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
HYPONATRAEMIC SYNDROME			
subjects affected / exposed	0 / 577 (0.00%)	1 / 575 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Selexipag	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	486 / 577 (84.23%)	544 / 575 (94.61%)	
Vascular disorders			
FLUSHING			
subjects affected / exposed	29 / 577 (5.03%)	69 / 575 (12.00%)	
occurrences (all)	31	80	
Cardiac disorders			
PALPITATIONS			
subjects affected / exposed	31 / 577 (5.37%)	32 / 575 (5.57%)	
occurrences (all)	41	40	
Nervous system disorders			

DIZZINESS			
subjects affected / exposed	85 / 577 (14.73%)	85 / 575 (14.78%)	
occurrences (all)	106	111	
HEADACHE			
subjects affected / exposed	189 / 577 (32.76%)	374 / 575 (65.04%)	
occurrences (all)	261	649	
SYNCOPE			
subjects affected / exposed	34 / 577 (5.89%)	30 / 575 (5.22%)	
occurrences (all)	42	35	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	28 / 577 (4.85%)	43 / 575 (7.48%)	
occurrences (all)	37	53	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	24 / 577 (4.16%)	29 / 575 (5.04%)	
occurrences (all)	27	33	
CHEST PAIN			
subjects affected / exposed	39 / 577 (6.76%)	34 / 575 (5.91%)	
occurrences (all)	54	37	
FATIGUE			
subjects affected / exposed	58 / 577 (10.05%)	46 / 575 (8.00%)	
occurrences (all)	72	54	
OEDEMA PERIPHERAL			
subjects affected / exposed	100 / 577 (17.33%)	77 / 575 (13.39%)	
occurrences (all)	138	90	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	29 / 577 (5.03%)	44 / 575 (7.65%)	
occurrences (all)	37	54	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	32 / 577 (5.55%)	34 / 575 (5.91%)	
occurrences (all)	38	39	
DIARRHOEA			
subjects affected / exposed	109 / 577 (18.89%)	242 / 575 (42.09%)	
occurrences (all)	137	375	

NAUSEA			
subjects affected / exposed	107 / 577 (18.54%)	192 / 575 (33.39%)	
occurrences (all)	136	265	
VOMITING			
subjects affected / exposed	48 / 577 (8.32%)	103 / 575 (17.91%)	
occurrences (all)	53	143	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	67 / 577 (11.61%)	56 / 575 (9.74%)	
occurrences (all)	87	67	
DYSPNOEA			
subjects affected / exposed	110 / 577 (19.06%)	79 / 575 (13.74%)	
occurrences (all)	143	100	
PULMONARY ARTERIAL HYPERTENSION			
subjects affected / exposed	84 / 577 (14.56%)	46 / 575 (8.00%)	
occurrences (all)	141	64	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	44 / 577 (7.63%)	62 / 575 (10.78%)	
occurrences (all)	57	82	
BACK PAIN			
subjects affected / exposed	35 / 577 (6.07%)	34 / 575 (5.91%)	
occurrences (all)	38	36	
MYALGIA			
subjects affected / exposed	34 / 577 (5.89%)	90 / 575 (15.65%)	
occurrences (all)	37	120	
PAIN IN EXTREMITY			
subjects affected / exposed	46 / 577 (7.97%)	95 / 575 (16.52%)	
occurrences (all)	62	142	
PAIN IN JAW			
subjects affected / exposed	36 / 577 (6.24%)	148 / 575 (25.74%)	
occurrences (all)	38	188	
Infections and infestations			
BRONCHITIS			

subjects affected / exposed	41 / 577 (7.11%)	42 / 575 (7.30%)	
occurrences (all)	49	46	
NASOPHARYNGITIS			
subjects affected / exposed	63 / 577 (10.92%)	75 / 575 (13.04%)	
occurrences (all)	95	105	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	79 / 577 (13.69%)	72 / 575 (12.52%)	
occurrences (all)	119	100	
URINARY TRACT INFECTION			
subjects affected / exposed	30 / 577 (5.20%)	24 / 575 (4.17%)	
occurrences (all)	34	30	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	19 / 577 (3.29%)	34 / 575 (5.91%)	
occurrences (all)	23	38	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 March 2010	- Merge of studies AC-065A301 and AC-065A302 into one study (AC-065A302 /GRIPHON) - Two primary endpoints were initially defined: time to clinical worsening (mortality / morbidity events) and change from baseline to week 16 in 6MWD. The latter was moved to the secondary endpoints and the time of assessment was slightly changed (from week 16 to week 26). In addition, for the analysis of the time to clinical worsening, subjects were to be censored 7 days after study treatment discontinuation, in accordance with FDA recommendations
20 December 2010	- Additional ECGs as recommended by the FDA - Deletion of the inclusion criteria related to "refrain from sun exposure" (phase I study did not indicate phototoxic potential) - Statistical clarification as requested by the FDA
11 May 2011	- Addition of thyroid markers monitoring - Addition of a sub-study for ophthalmological evaluations
14 December 2011	- Increase in the assumed hazard ratio for the primary endpoint (0.5729 to 0.65) and the sample size (670 to 1150) and the sample size (670 to 1150) and increase of the number of MM events (202 to 331) - Addition of a futility and efficacy interim analysis after 202 M/M events - M/M events with onset date up to 16 AUG 11 to be censored for primary endpoint analysis NOTE: All the events, including those < 16AUG11 are reported in the present results summary since the results were virtually identical with and without censoring
23 January 2013	- Wording of the primary endpoint "clinical worsening event" was changed to "mortality/morbidity event" - Introduction of a post-treatment observation period (PTOP) data collection - Addition of an ophthalmological safety board, an expert medical review committee (PAH etiology) and expansion of the CEC role - Addition of exploratory endpoints including: time to first MM event up to study closure (SC), time to first MM event (excluding disease progression) up to SC, time to death or hospitalization due to PAH up to 7 days after EOT or up to SC - Statistical clarifications and modifications but the primary statistical analysis of the primary efficacy endpoint was not affected

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26699168