



Clinical trial results:

Long term single-arm open-label study, to assess the safety and tolerability of selexipag

(ACT-293987) in patients with pulmonary arterial hypertension

Summary

EudraCT number	2009-014992-31
Trial protocol	BE FR ES SE DK GB IE PL AT HU DE SK CZ GR NL IT
Global end of trial date	29 September 2021

Results information

Result version number	v1 (current)
This version publication date	09 September 2022
First version publication date	09 September 2022

Trial information

Trial identification

Sponsor protocol code	AC-065A303
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01112306
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, 4123
Public contact	Clinical Registry Group, Actelion Pharmaceuticals Ltd, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Actelion Pharmaceuticals Ltd, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 September 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to assess long-term safety and tolerability of selexipag in subjects with pulmonary arterial hypertension (PAH).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 June 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 20
Country: Number of subjects enrolled	Australia: 37
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	Belarus: 34
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Chile: 31
Country: Number of subjects enrolled	China: 113
Country: Number of subjects enrolled	Colombia: 3
Country: Number of subjects enrolled	Czechia: 11
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	India: 15
Country: Number of subjects enrolled	Ireland: 4

Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Korea, Republic of: 11
Country: Number of subjects enrolled	Mexico: 20
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Peru: 6
Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Romania: 9
Country: Number of subjects enrolled	Russian Federation: 72
Country: Number of subjects enrolled	Singapore: 8
Country: Number of subjects enrolled	Serbia: 10
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Sweden: 10
Country: Number of subjects enrolled	Thailand: 4
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	Taiwan: 11
Country: Number of subjects enrolled	Ukraine: 35
Country: Number of subjects enrolled	United States: 80
Worldwide total number of subjects	709
EEA total number of subjects	154

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)	597
From 65 to 84 years	112
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 709 subjects were enrolled in the study. Out of the 709 subjects, 424 subjects completed the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Selexipag
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Arm description:

Subjects with pulmonary arterial hypertension (PAH) who completed the double-blind AC-065A302 GRIPHON study or experienced a morbidity/mortality event in that study, entered in this open label (OL) study. Subjects who received selexipag in GRIPHON continued to receive selexipag at the same dose (200 micrograms [mcg], twice daily [bid] up to 1600 mcg bid based on individual maximum tolerated dose) in this OL study. Subjects who were on placebo or experienced a morbidity/mortality event in GRIPHON entered the titration period of this OL-study and received lowest dose of selexipag (200 mcg, bid) and dose was titrated up to 1600 mcg bid, based on the individual maximum tolerated dose. Each subject received study drug from Day 1 until the earliest of a) selexipag became commercially available in this indication in subject's country, b) sponsor decided to stop current study, or c) subject/investigator decided to discontinue study intervention (up to 10.5 years).

Arm type	Experimental
Investigational medicinal product name	Selexipag
Investigational medicinal product code	
Other name	JNJ-67896049 ACT-293987
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Selexipag (up-titrated from 200 mcg bid to 1600 mcg bid based on individual maximum tolerated dose) was administered bid with food from Day 1 until the earliest of a) selexipag became commercially available in this indication in subject's country, b) sponsor decided to stop current study, or c) subject/investigator decided to discontinue study intervention (up to 10.5 years).

Number of subjects in period 1	Selexipag
Started	709
Completed	424
Not completed	285
Adverse event, serious fatal	175
Consent withdrawn by subject	31
Unspecified	70
Lost to follow-up	9

Baseline characteristics

Reporting groups

Reporting group title	Selexipag
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Reporting group description:

Subjects with pulmonary arterial hypertension (PAH) who completed the double-blind AC-065A302 GRIPHON study or experienced a morbidity/mortality event in that study, entered in this open label (OL) study. Subjects who received selexipag in GRIPHON continued to receive selexipag at the same dose (200 micrograms [mcg], twice daily [bid] up to 1600 mcg bid based on individual maximum tolerated dose) in this OL study. Subjects who were on placebo or experienced a morbidity/mortality event in GRIPHON entered the titration period of this OL-study and received lowest dose of selexipag (200 mcg, bid) and dose was titrated up to 1600 mcg bid, based on the individual maximum tolerated dose. Each subject received study drug from Day 1 until the earliest of a) selexipag became commercially available in this indication in subject's country, b) sponsor decided to stop current study, or c) subject/investigator decided to discontinue study intervention (up to 10.5 years).

Reporting group values	Selexipag	Total	
Number of subjects	709	709	
Title for AgeCategorical Units: subjects			
Adolescents: 12-<18 yrs	0	0	
Adults: >= 18 yrs	709	709	
Title for AgeContinuous Units: years			
arithmetic mean	47.9		
standard deviation	± 15.19	-	
Title for Gender Units: subjects			
Female	590	590	
Male	119	119	

End points

End points reporting groups

Reporting group title	Selexipag
Reporting group description:	
Subjects with pulmonary arterial hypertension (PAH) who completed the double-blind AC-065A302 GRIPHON study or experienced a morbidity/mortality event in that study, entered in this open label (OL) study. Subjects who received selexipag in GRIPHON continued to receive selexipag at the same dose (200 micrograms [mcg], twice daily [bid] up to 1600 mcg bid based on individual maximum tolerated dose) in this OL study. Subjects who were on placebo or experienced a morbidity/mortality event in GRIPHON entered the titration period of this OL-study and received lowest dose of selexipag (200 mcg, bid) and dose was titrated up to 1600 mcg bid, based on the individual maximum tolerated dose. Each subject received study drug from Day 1 until the earliest of a) selexipag became commercially available in this indication in subject's country, b) sponsor decided to stop current study, or c) subject/investigator decided to discontinue study intervention (up to 10.5 years).	

Primary: Number of Subjects with Treatment-emergent Adverse Events (TEAEs) up to 3 days After Study Intervention Discontinuation

End point title	Number of Subjects with Treatment-emergent Adverse Events (TEAEs) up to 3 days After Study Intervention Discontinuation ^[1]
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End point description:

An adverse event (AE) is any untoward medical event that occurs in a subject administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. A TEAE is any AE temporally associated with the use of study drug (from study drug initiation until 3 days after study drug discontinuation), whether or not considered related to the study drug. The safety set included all randomised subjects who received at least 1 dose of selexipag or placebo.

End point type	Primary
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End point timeframe:

Up to 3 days after drug discontinuation (Up to 10.5 years)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No inferential statistics was planned for this primary endpoint.

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	709			
Units: subjects	684			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with TEAEs Leading to Permanent Discontinuation of Study Intervention

End point title	Number of Subjects with TEAEs Leading to Permanent Discontinuation of Study Intervention ^[2]
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End point description:

An adverse event (AE) is any untoward medical event that occurs in a subject administered an

investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. A TEAE is any AE temporally associated with the use of study drug (from study drug initiation until 3 days after study drug discontinuation), whether or not considered related to the study drug. The safety set included all randomised subjects who received at least 1 dose of selexipag or placebo.

End point type	Primary
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End point timeframe:

Up to 10.5 years

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No inferential statistics was planned for this primary endpoint.

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	709			
Units: subjects	129			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Treatment-emergent Serious Adverse Events (TESAEs) up to 3 days After Study Intervention Discontinuation

End point title	Number of Subjects with Treatment-emergent Serious Adverse Events (TESAEs) up to 3 days After Study Intervention Discontinuation ^[3]
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End point description:

An adverse event is any untoward medical event that occurs in a subject administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. SAE is any AE that results in: death, persistent or significant disability/incapacity, requires inpatient hospitalisation or prolongation of existing hospitalisation, is life-threatening experience, is a congenital anomaly/birth defect and may jeopardise subject and/or may require medical or surgical intervention to prevent one of the outcomes listed above. Those SAEs occurring during study drug administration, that is, between study drug initiation and three days after study drug discontinuation, are defined as treatment-emergent SAEs. The safety set included all randomised subjects who received at least 1 dose of selexipag or placebo.

End point type	Primary
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End point timeframe:

Up to 3 days after drug discontinuation (Up to 10.5 years)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No inferential statistics was planned for this primary endpoint.

End point values	Selexipag			
Subject group type	Reporting group			
Number of subjects analysed	709			
Units: subjects	420			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 10.5 years for serious and other (non-serious) adverse events and up to 11.2 years for all-cause mortality

Adverse event reporting additional description:

The safety set included all randomised subjects who received at least 1 dose of selexipag or placebo.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	Selexipag
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Reporting group description:

Subjects with pulmonary arterial hypertension (PAH) who completed the double-blind AC-065A302 GRIPHON study or experienced a morbidity/mortality event in that study, entered in this open label (OL) study. Subjects who received selexipag in GRIPHON continued to receive selexipag at the same dose (200 micrograms [mcg], twice daily [bid] up to 1600 mcg bid based on individual maximum tolerated dose) in this OL study. Subjects who were on placebo or experienced a morbidity/mortality event in GRIPHON entered the titration period of this OL-study and received lowest dose of selexipag (200 mcg, bid) and dose was titrated up to 1600 mcg bid, based on the individual maximum tolerated dose. Each subject received study drug from Day 1 until the earliest of a) selexipag became commercially available in this indication in subject's country, b) sponsor decided to stop current study, or c) subject/investigator decided to discontinue study intervention (up to 10.5 years).

Serious adverse events	Selexipag		
Total subjects affected by serious adverse events			
subjects affected / exposed	420 / 709 (59.24%)		
number of deaths (all causes)	186		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of Colon			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Benign Salivary Gland Neoplasm			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Breast Cancer Metastatic			

subjects affected / exposed	2 / 709 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Breast Cancer Recurrent				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Carcinoid Tumour of the Stomach				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endometrial Cancer Stage I				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endometrial Adenocarcinoma				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Extranodal Marginal Zone B-Cell Lymphoma (Malt Type)				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infected Neoplasm				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatocellular Carcinoma				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Lung Adenocarcinoma				

subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung Neoplasm Malignant			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to the Mediastinum			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nodal Marginal Zone B-Cell Lymphoma			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Ovarian Germ Cell Teratoma Benign			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Papillary Thyroid Cancer			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine Leiomyoma			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Circulatory Collapse			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Deep Vein Thrombosis			

subjects affected / exposed	3 / 709 (0.42%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	6 / 709 (0.85%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Hypovolaemic Shock			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Orthostatic Hypotension			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral Ischaemia			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral Arterial Occlusive Disease			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vasculitis			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Superior Vena Cava Perforation			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Venous Thrombosis Limb			

subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Benign Breast Lump Removal			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Balloon Atrial Septostomy			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast Conserving Surgery			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary Arterial Stent Insertion			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug Therapy			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac Pacemaker Insertion			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary Angioplasty			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric Bypass			

subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fasciotomy				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Heart and Lung Transplant				
subjects affected / exposed	2 / 709 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hip Arthroplasty				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Knee Operation				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung Transplant				
subjects affected / exposed	5 / 709 (0.71%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Nephrectomy				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian Cystectomy				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Packed Red Blood Cell Transfusion				

subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rehabilitation Therapy			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Percutaneous Coronary Intervention			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transfusion			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Varicose Vein Operation			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular Operation			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion Missed			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy			
subjects affected / exposed	5 / 709 (0.71%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Abortion Spontaneous			

subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Catheter Site Erythema			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Catheter Site Thrombosis			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest Discomfort			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Chest Pain			
subjects affected / exposed	7 / 709 (0.99%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	3 / 709 (0.42%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Drowning			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Drug Interaction			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug Ineffective			

subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Euthanasia				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Gait Disturbance				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Generalised Oedema				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple Organ Dysfunction Syndrome				
subjects affected / exposed	8 / 709 (1.13%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 7			
Oedema Peripheral				
subjects affected / exposed	4 / 709 (0.56%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Peripheral Swelling				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Organ Failure				

subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	5 / 709 (0.71%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Sudden Cardiac Death			
subjects affected / exposed	3 / 709 (0.42%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Sudden Death			
subjects affected / exposed	14 / 709 (1.97%)		
occurrences causally related to treatment / all	0 / 14		
deaths causally related to treatment / all	0 / 14		
Systemic Inflammatory Response Syndrome			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Withdrawal Syndrome			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Immune system disorders			
Amyloidosis			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Uterine Haemorrhage			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vaginal Haemorrhage			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute Pulmonary Oedema			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Asthma			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute Respiratory Failure			
subjects affected / exposed	5 / 709 (0.71%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 5		
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Chronic Respiratory Failure			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Dyspnoea			
subjects affected / exposed	18 / 709 (2.54%)		
occurrences causally related to treatment / all	0 / 21		
deaths causally related to treatment / all	0 / 0		

Dyspnoea Exertional				
subjects affected / exposed	2 / 709 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	10 / 709 (1.41%)			
occurrences causally related to treatment / all	1 / 13			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypersensitivity Pneumonitis				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lower Respiratory Tract Inflammation				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	4 / 709 (0.56%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Lupus Pneumonitis				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleuritic Pain				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleurisy				

subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary Alveolar Haemorrhage			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pulmonary Arterial Hypertension			
subjects affected / exposed	169 / 709 (23.84%)		
occurrences causally related to treatment / all	2 / 220		
deaths causally related to treatment / all	1 / 66		
Pulmonary Artery Dilatation			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary Artery Aneurysm			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary Embolism			
subjects affected / exposed	8 / 709 (1.13%)		
occurrences causally related to treatment / all	0 / 12		
deaths causally related to treatment / all	0 / 4		
Pulmonary Hypertension			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Pulmonary Oedema			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Pulmonary Mass			

subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory Distress			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory Failure			
subjects affected / exposed	4 / 709 (0.56%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		
Psychiatric disorders			
Acute Psychosis			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug Dependence			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anxiety			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Major Depression			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Suicide Attempt			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

Bile Duct Stone				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	2 / 709 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Cardiac Cirrhosis				
subjects affected / exposed	2 / 709 (0.28%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Cholecystitis Acute				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cirrhosis Alcoholic				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cholelithiasis				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Drug-Induced Liver Injury				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic Failure				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Jaundice				

subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Activated Partial Thromboplastin Time Prolonged			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anticoagulation Drug Level above Therapeutic			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood Uric Acid Increased			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Biopsy Kidney			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Catheterisation Cardiac			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haemoglobin Decreased			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
International Normalised Ratio Increased			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Investigation				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
N-Terminal Prohormone Brain Natriuretic Peptide Increased				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Precancerous Cells Present				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transplant Evaluation				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prothrombin Time Prolonged				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Weight Decreased				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Accident				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anaesthetic Complication				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

Ankle Fracture				
subjects affected / exposed	3 / 709 (0.42%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	8 / 709 (1.13%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 1			
Contusion				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Concussion				
subjects affected / exposed	2 / 709 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Head Injury				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fractured Sacrum				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femoral Neck Fracture				
subjects affected / exposed	2 / 709 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Humerus Fracture				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intentional Overdose				

subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jaw Fracture			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint Dislocation			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic Fracture			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Poisoning			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Radius Fracture			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post Procedural Haemorrhage			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Reactive Gastropathy			

subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Road Traffic Accident				
subjects affected / exposed	2 / 709 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Rib Fracture				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin Laceration				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Soft Tissue Injury				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal Compression Fracture				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subcutaneous Haematoma				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal Fracture				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Toxicity to Various Agents				

subjects affected / exposed	3 / 709 (0.42%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Traumatic Haematoma			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper Limb Fracture			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular Pseudoaneurysm			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Dermoid Cyst			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic Arteriovenous Malformation			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Acute Myocardial Infarction			
subjects affected / exposed	4 / 709 (0.56%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		

Acute Right Ventricular Failure subjects affected / exposed	11 / 709 (1.55%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 11			
Angina Pectoris subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aortic Valve Stenosis subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arrhythmia subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial Fibrillation subjects affected / exposed	17 / 709 (2.40%)			
occurrences causally related to treatment / all	0 / 23			
deaths causally related to treatment / all	0 / 0			
Atrial Tachycardia subjects affected / exposed	2 / 709 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Atrial Flutter subjects affected / exposed	8 / 709 (1.13%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 1			
Atrioventricular Block subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrioventricular Block Second Degree				

subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrioventricular Block Complete			
subjects affected / exposed	3 / 709 (0.42%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac Arrest			
subjects affected / exposed	13 / 709 (1.83%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 13		
Cardiac Failure			
subjects affected / exposed	8 / 709 (1.13%)		
occurrences causally related to treatment / all	0 / 12		
deaths causally related to treatment / all	0 / 2		
Cardiac Failure Acute			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac Failure Congestive			
subjects affected / exposed	4 / 709 (0.56%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		
Cardiac Failure Chronic			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiopulmonary Failure			
subjects affected / exposed	8 / 709 (1.13%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 8		
Cardiogenic Shock			

subjects affected / exposed	9 / 709 (1.27%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 8		
Cardio-Respiratory Arrest			
subjects affected / exposed	5 / 709 (0.71%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 5		
Cardiorenal Syndrome			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiovascular Insufficiency			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Chronic Left Ventricular Failure			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic Right Ventricular Failure			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Cor Pulmonale			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cor Pulmonale Acute			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial Infarction			

subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Left Ventricular Failure			
subjects affected / exposed	4 / 709 (0.56%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Coronary Artery Disease			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pericardial Effusion			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Right Ventricular Dysfunction			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Right Ventricular Failure			
subjects affected / exposed	93 / 709 (13.12%)		
occurrences causally related to treatment / all	1 / 163		
deaths causally related to treatment / all	0 / 39		
Supraventricular Tachycardia			
subjects affected / exposed	4 / 709 (0.56%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 1		
Tricuspid Valve Incompetence			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular Tachyarrhythmia			

subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral Infarction			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Carotid Artery Occlusion			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intracranial Haematoma			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	4 / 709 (0.56%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Ischaemic Stroke			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	3 / 709 (0.42%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			

subjects affected / exposed	18 / 709 (2.54%)		
occurrences causally related to treatment / all	0 / 25		
deaths causally related to treatment / all	0 / 0		
Vocal Cord Paralysis			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient Ischaemic Attack			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 709 (1.27%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 1		
Anaemia Vitamin B12 Deficiency			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone Marrow Failure			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood Loss Anaemia			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Disseminated Intravascular Coagulation			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Immune Thrombocytopenic Purpura			

subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Iron Deficiency Anaemia			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pseudolymphoma			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy Mediastinal			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			

Diabetic Retinopathy			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Astigmatism			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Glaucoma			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Abdominal Hernia			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal Pain			
subjects affected / exposed	4 / 709 (0.56%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Abdominal Wall Haematoma			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal Pain Lower			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic Gastritis			

subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	6 / 709 (0.85%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 1		
Colitis			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	12 / 709 (1.69%)		
occurrences causally related to treatment / all	3 / 13		
deaths causally related to treatment / all	0 / 2		
Constipation			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticular Perforation			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocolitis			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis Haemorrhagic			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric Ulcer			

subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal Haemorrhage				
subjects affected / exposed	9 / 709 (1.27%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 2			
Gastrointestinal Motility Disorder				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus Paralytic				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal Haemorrhage				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large Intestinal Haemorrhage				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large Intestine Polyp				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Melaena				

subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Obstructive Pancreatitis			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal Haemorrhage			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis Acute			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal Haemorrhage			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	3 / 709 (0.42%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Skin and subcutaneous tissue disorders			
Skin Necrosis			

subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin Ulcer			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Chronic Kidney Disease			
subjects affected / exposed	3 / 709 (0.42%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Acute Kidney Injury			
subjects affected / exposed	6 / 709 (0.85%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Cystitis Haemorrhagic			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Glomerulonephritis Chronic			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic Nephropathy			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Lupus Nephritis			

subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal Failure			
subjects affected / exposed	4 / 709 (0.56%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Proteinuria			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal Haematoma			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tubulointerstitial Nephritis			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal Impairment			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary Retention			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenocortical Insufficiency Acute			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basedow's Disease			

subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperthyroidism			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thyroiditis Subacute			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Fracture Malunion			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mixed Connective Tissue Disease			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematoma Muscle			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neck Pain			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			

subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rheumatoid Arthritis			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Systemic Lupus Erythematosus			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Still's Disease			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 1		
Systemic Scleroderma			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess Bacterial			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abscess Limb			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Appendicitis			
subjects affected / exposed	3 / 709 (0.42%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Anal Abscess			

subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Actinomycotic Pulmonary Infection			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacterial Abdominal Infection			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Atypical Pneumonia			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis Perforated			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Bacterial Sepsis			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Bronchitis			
subjects affected / exposed	11 / 709 (1.55%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	6 / 709 (0.85%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Clostridium Difficile Colitis			

subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Colonic Abscess				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Corona Virus Infection				
subjects affected / exposed	4 / 709 (0.56%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Complicated Appendicitis				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dengue Fever				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Disseminated Tuberculosis				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Empyema				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endocarditis				

subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Enterobacter Sepsis			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Escherichia Sepsis			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	3 / 709 (0.42%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Escherichia Urinary Tract Infection			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis Norovirus			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis Clostridial			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal Infection			

subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
H1n1 Influenza				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Herpes Zoster				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic Pneumonia				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Haematoma Infection				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infective Tenosynovitis				
subjects affected / exposed	2 / 709 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	2 / 709 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Influenza				
subjects affected / exposed	1 / 709 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower Respiratory Tract Infection				

subjects affected / exposed	8 / 709 (1.13%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 0		
Lung Infection			
subjects affected / exposed	5 / 709 (0.71%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
Nasopharyngitis			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Osteomyelitis			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis Media Bacterial			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis Bacterial			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	3 / 709 (0.42%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Pneumonia			
subjects affected / exposed	50 / 709 (7.05%)		
occurrences causally related to treatment / all	0 / 58		
deaths causally related to treatment / all	0 / 10		
Pneumonia Bacterial			

subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Pneumonia Viral			
subjects affected / exposed	3 / 709 (0.42%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Postoperative Wound Infection			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis Acute			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pyoderma			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Sepsis			
subjects affected / exposed	10 / 709 (1.41%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 4		
Rhinitis			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory Tract Infection			

subjects affected / exposed	4 / 709 (0.56%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 1		
Septic Shock			
subjects affected / exposed	3 / 709 (0.42%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Sialoadenitis			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Soft Tissue Infection			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Staphylococcal Sepsis			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Tracheobronchitis			
subjects affected / exposed	2 / 709 (0.28%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Upper Respiratory Tract Infection			
subjects affected / exposed	4 / 709 (0.56%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Infection			
subjects affected / exposed	4 / 709 (0.56%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Viral Infection			

subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound Infection			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Fluid Overload			
subjects affected / exposed	3 / 709 (0.42%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Fluid Retention			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoproteinaemia			

subjects affected / exposed	1 / 709 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Selexipag		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	598 / 709 (84.34%)		
Vascular disorders			
Flushing			
subjects affected / exposed	49 / 709 (6.91%)		
occurrences (all)	54		
Hypotension			
subjects affected / exposed	38 / 709 (5.36%)		
occurrences (all)	48		
Cardiac disorders			
Palpitations			
subjects affected / exposed	43 / 709 (6.06%)		
occurrences (all)	48		
Nervous system disorders			
Dizziness			
subjects affected / exposed	71 / 709 (10.01%)		
occurrences (all)	88		
Headache			
subjects affected / exposed	328 / 709 (46.26%)		
occurrences (all)	469		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	65 / 709 (9.17%)		
occurrences (all)	78		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	44 / 709 (6.21%)		
occurrences (all)	48		
Oedema Peripheral			

subjects affected / exposed	90 / 709 (12.69%)		
occurrences (all)	104		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	209 / 709 (29.48%)		
occurrences (all)	274		
Nausea			
subjects affected / exposed	135 / 709 (19.04%)		
occurrences (all)	171		
Vomiting			
subjects affected / exposed	74 / 709 (10.44%)		
occurrences (all)	90		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	80 / 709 (11.28%)		
occurrences (all)	96		
Dyspnoea			
subjects affected / exposed	76 / 709 (10.72%)		
occurrences (all)	99		
Pulmonary Arterial Hypertension			
subjects affected / exposed	68 / 709 (9.59%)		
occurrences (all)	77		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	65 / 709 (9.17%)		
occurrences (all)	75		
Myalgia			
subjects affected / exposed	68 / 709 (9.59%)		
occurrences (all)	92		
Pain in Extremity			
subjects affected / exposed	78 / 709 (11.00%)		
occurrences (all)	97		
Pain in Jaw			
subjects affected / exposed	130 / 709 (18.34%)		
occurrences (all)	153		
Infections and infestations			

Bronchitis			
subjects affected / exposed	59 / 709 (8.32%)		
occurrences (all)	76		
Urinary Tract Infection			
subjects affected / exposed	42 / 709 (5.92%)		
occurrences (all)	54		
Upper Respiratory Tract Infection			
subjects affected / exposed	84 / 709 (11.85%)		
occurrences (all)	130		
Nasopharyngitis			
subjects affected / exposed	88 / 709 (12.41%)		
occurrences (all)	125		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	44 / 709 (6.21%)		
occurrences (all)	54		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2010	The purpose of this amendment was: the double-blind studies AC-065A301 and AC-065A302 (2009-014490-41) were merged into a single study and all references were replaced by the reference to the merged protocol AC-065A302; subjects who experienced a Critical Event Committee (CEC)-confirmed clinical worsening event during study AC-065A302 could only enter study AC-065A303 after their Week 16 visit of study AC-065A302 and after written approval from the sponsor. These restrictions were removed; a time limit of 2 weeks after the last visit in study AC-065A302 was introduced for entering study AC-065A303; and clarification that prostacyclin and prostanoid therapy were prohibited not only during study AC-065A303 but also during the transition period between study AC-065A302 and study AC-065A303.
20 December 2010	The purpose of this amendment was: the precautionary wording regarding sun exposure was removed and the Independent Data Monitoring Committee reviewing unblinded safety data of Study AC-065A302 was also assigned the review of safety data from the study AC-065A303.
19 April 2013	The purpose of this amendment was: sample size was increased from 670 up to a maximum of 1150 and collection of safety data in the clinical database was extended to vital signs, body weight, concomitant medications, and laboratory results; guidance for management of subjects with liver impairment was provided; and eligibility of study AC-065A302 subjects to study AC-065A303 was extended to subjects with worsening of pulmonary arterial hypertension (PAH) during the treatment extension period of study AC-065A302.
16 March 2015	The purpose of this amendment was: the possibility to up-titrate selexipag at unscheduled visits (for subjects who had not reached the maximum allowed dose) was introduced; the overall duration of study AC-065A303 was changed from "until the approval of selexipag in PAH" to "until selexipag is commercially available"; temporary concomitant use of selexipag and intravenous (IV), subcutaneous (SC), or inhaled prostacyclin and prostacyclin analogs was allowed when deemed medically indicated for the subject; and a discontinuation criterion for subjects diagnosed with pulmonary venoocclusive disease (PVOD) was introduced.
15 June 2016	The purpose of this amendment was: disbandment of the Data Monitoring Committee involved in study AC-065A302 and Ophthalmology Safety Board as of 01 July 2016; and the reference to the selexipag Investigator Brochure (IB) Section 6 was replaced with the complete list of adverse events.
25 January 2017	The purpose of this amendment was: further to new drug-drug interaction study results, concomitant administration of strong cytochrome P450 (CYP)2C8 inhibitors such as gemfibrozil was to be avoided and in case of concomitant administration of rifampicin, dose adjustment of selexipag could be required.
30 June 2017	The purpose of this amendment was to: contraindication of strong CYP2C8 inhibitors such as gemfibrozil in accordance with IB Version 11 was added; and information on the lack of studies to determine the effect of moderate inhibitors of CYP2C8, and strong inhibitors of UGT1A3 and UGT2B7 on the exposure to selexipag or its active metabolite was added.

06 February 2019	The purpose of this amendment was: Guidance for concomitant administration of selexipag and moderate inhibitors of CYP2C8 was updated based on Phase 1 study AC-065-117, in accordance with IB Version 13; clinical information section was updated to include reference to the recently completed studies along with the results in accordance with IB Version 13; statistical section was updated according to International Council for Harmonisation E6 guideline; and the data collection section was updated to allow the use of a standard ballpoint pen to complete the Case Report Forms (CRF).
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The open-label, uncontrolled design, additional PAH-specific treatments in limited subjects for limited time, a variable study duration due to commercial selexipag availability and limitation of safety data reporting in China by 20-Dec-2019.

Notes: