

**Clinical trial results:****Long-term Single-arm Open Label Extension Study of the SERAPHIN Study, to Assess the Safety and Tolerability of Macitentan/ACT-064992 in Patients with Symptomatic Pulmonary Arterial Hypertension****Summary**

EudraCT number	2007-003694-27
Trial protocol	GB DE NL FR FI SE AT BE DK SK PT IT PL BG
Global end of trial date	07 December 2020

Results information

Result version number	v1 (current)
This version publication date	20 June 2021
First version publication date	20 June 2021

Trial information**Trial identification**

Sponsor protocol code	AC-055-303
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00667823
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 December 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of the trial was to assess long-term safety and tolerability of macitentan in subjects with symptomatic 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. Safety assessments include adverse events, deaths and clinical laboratory test results.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 October 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 32
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	Belarus: 21
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Chile: 24
Country: Number of subjects enrolled	China: 74
Country: Number of subjects enrolled	Colombia: 7
Country: Number of subjects enrolled	Germany: 27
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	India: 30
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Mexico: 33
Country: Number of subjects enrolled	Malaysia: 6

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Peru: 4
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Romania: 12
Country: Number of subjects enrolled	Russian Federation: 54
Country: Number of subjects enrolled	Singapore: 12
Country: Number of subjects enrolled	Serbia: 13
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Thailand: 19
Country: Number of subjects enrolled	Taiwan: 14
Country: Number of subjects enrolled	Ukraine: 12
Country: Number of subjects enrolled	United States: 49
Country: Number of subjects enrolled	South Africa: 17
Worldwide total number of subjects	550
EEA total number of subjects	94

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)	6
Adults (18-64 years)	459
From 65 to 84 years	84
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 550 subjects were enrolled in the study. Out of the 550 subjects, 339 subjects completed the study.

Period 1

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

Arms

Arm title	Macitentan 10 mg
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Arm description:

Subjects with symptomatic pulmonary arterial hypertension (PAH) who completed or have experienced a morbidity/clinical worsening of PAH in the study AC-055-302 and opted to continue this open label extension study received macitentan oral tablet, 10 milligram (mg) once daily from Day 1 up to end of study (Up to 12 years) which depends on following a). transition to commercially available macitentan in the subjects country b). the sponsor decided to stop the OL study, and c). the subjects or investigators or sponsors decision to discontinue study treatment.

Arm type	Experimental
Investigational medicinal product name	Macitentan
Investigational medicinal product code	
Other name	ACT-064992
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Macitentan 10 mg tablet was administered once daily from Day 1 up to end of study (Up to 12 years) which depends on following a). transition to commercially available macitentan in the subjects country b). the sponsor decided to stop the OL study, and c). the subjects or investigators or sponsors decision to discontinue study treatment.

Number of subjects in period 1	Macitentan 10 mg
Started	550
Completed	339
Not completed	211
Adverse event, serious fatal	177
Missing (completion page missing)	2
Adverse event, non-fatal	7
Other	8
Lost to follow-up	5
Withdrawal by subject	12

Baseline characteristics

Reporting groups

Reporting group title	Macitentan 10 mg
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Reporting group description:

Subjects with symptomatic pulmonary arterial hypertension (PAH) who completed or have experienced a morbidity/clinical worsening of PAH in the study AC-055-302 and opted to continue this open label extension study received macitentan oral tablet, 10 milligram (mg) once daily from Day 1 up to end of study (Up to 12 years) which depends on following a). transition to commercially available macitentan in the subjects country b). the sponsor decided to stop the OL study, and c). the subjects or investigators or sponsors decision to discontinue study treatment.

Reporting group values	Macitentan 10 mg	Total	
Number of subjects	550	550	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	6	6	
Adults (18-64 years)	459	459	
From 65 to 84 years	84	84	
85 years and over	1	1	
Title for AgeContinuous Units: years			
arithmetic mean	47.7		
standard deviation	± 15.67	-	
Title for Gender Units: subjects			
Female	440	440	
Male	110	110	

End points

End points reporting groups

Reporting group title	Macitentan 10 mg
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Reporting group description:

Subjects with symptomatic pulmonary arterial hypertension (PAH) who completed or have experienced a morbidity/clinical worsening of PAH in the study AC-055-302 and opted to continue this open label extension study received macitentan oral tablet, 10 milligram (mg) once daily from Day 1 up to end of study (Up to 12 years) which depends on following a). transition to commercially available macitentan in the subjects country b). the sponsor decided to stop the OL study, and c). the subjects or investigators or sponsors decision to discontinue study treatment.

Primary: Number of Subjects with Treatment Emergent Adverse Events (TEAEs) up to 28 Days After Study Treatment Discontinuation

End point title	Number of Subjects with Treatment Emergent Adverse Events (TEAEs) up to 28 Days After Study Treatment Discontinuation ^[1]
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End point description:

An adverse event (AE) is any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. TEAE are defined as AEs with onset during the treatment period or that are a consequence of a pre-existing condition that has worsened since baseline. The safety analysis set (SAF) included all subjects who received at least 1 dose of macitentan 10 milligram (mg).

End point type	Primary
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End point timeframe:

Up to 28 days after study treatment discontinuation (Up to 12 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	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	550			
Units: Subjects	527			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Death up to 28 Days After Study Treatment Discontinuation

End point title	Number of Subjects with Death up to 28 Days After Study Treatment Discontinuation ^[2]
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End point description:

Number of subjects with deaths up to 28 days after study treatment discontinuation were reported. The safety analysis set (SAF) included all subjects who received at least 1 dose of macitentan 10 mg.

End point type	Primary
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End point timeframe:

Up to 28 days after study treatment discontinuation (Up to 12 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	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	550			
Units: Subjects	175			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Treatment Emergent Serious Adverse Events (TESAEs) up to 28 Days After Study Treatment Discontinuation

End point title	Number of Subjects with Treatment Emergent Serious Adverse Events (TESAEs) up to 28 Days After Study Treatment Discontinuation ^[3]
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End point description:

An adverse event (AE) is any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. TEAE are defined as AEs with onset during the treatment period or that are a consequence of a pre-existing condition that has worsened since baseline. A SAE is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly; medically significant, or requires intervention to prevent at least one of the outcomes listed above. The safety analysis set (SAF) included all subjects who received at least 1 dose of macitentan 10 mg.

End point type	Primary
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End point timeframe:

Up to 28 days after study treatment discontinuation (Up to 12 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	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	550			
Units: Subjects	354			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with AEs Leading to Premature and Permanent Discontinuation of Study Treatment

End point title	Number of Subjects with AEs Leading to Premature and Permanent Discontinuation of Study Treatment ^[4]
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End point description:

Number of subjects with AEs leading to premature and permanent discontinuation of study treatment were reported. An adverse event (AE) is any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. The safety analysis set (SAF) included all subjects who received at least 1 dose of macitentan 10 mg.

End point type Primary

End point timeframe:

Up to 28 days after study treatment discontinuation (Up to 12 years)

Notes:

[4] - 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	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	550			
Units: Subjects	62			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Treatment Emergent Abnormal Liver Tests up to 28 Days After Study Treatment Discontinuation

End point title Number of Subjects with Treatment Emergent Abnormal Liver Tests up to 28 Days After Study Treatment Discontinuation^[5]

End point description:

Number of subjects with treatment-emergent abnormal liver tests : Alanine aminotransferase (ALT) greater than or equal to (\geq) 3*upper limit of normal (ULN) or aspartate aminotransferase (AST) \geq 3*ULN, ALT \geq 5* ULN or AST \geq 5*ULN, ALT \geq 8*ULN or AST \geq 8*ULN, total bilirubin (TBIL) \geq 2*ULN, [(ALT \geq 3*ULN or AST \geq 3*ULN) and TBIL \geq 2*ULN at any time] were reported. The safety analysis set (SAF) included all subjects who received at least 1 dose of macitentan 10 mg.

End point type Primary

End point timeframe:

Up to 28 days after study treatment discontinuation (Up to 12 years)

Notes:

[5] - 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	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	550			
Units: Subjects				
ALT or AST $>$ 3*ULN	45			
ALT or AST $>$ 5*ULN	20			
ALT or AST $>$ 8*ULN	11			
TBIL $>$ 2*ULN	75			
(ALT or AST $>$ 3*ULN), (TBIL $>$ 2*ULN at any time)	8			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Treatment Emergent Hemoglobin Abnormality up to 28 Days After Study Treatment Discontinuation

End point title	Number of Subjects with Treatment Emergent Hemoglobin Abnormality up to 28 Days After Study Treatment Discontinuation ^[6]
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End point description:

Number of subjects with treatment-emergent hemoglobin (HGB) abnormality up to 28 days after study treatment discontinuation were reported. The safety analysis set (SAF) included all subjects who received at least 1 dose of macitentan 10 mg.

End point type	Primary
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End point timeframe:

Up to 28 days after treatment discontinuation (Up to 12 years)

Notes:

[6] - 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	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	550			
Units: Subjects				
HGB <= 80 gram/Liter (g/L)	33			
HGB <= 100 g/L	98			
HGB decrease from baseline >= 20 g/L	188			
HGB decrease from baseline >= 50 g/L	29			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to End of treatment plus 28 days (safety follow-up) [Up to 12 years]

Adverse event reporting additional description:

The safety analysis set (SAF) included all subjects who received at least 1 dose of macitentan 10 milligram (mg).

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Macitentan 10 mg
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Reporting group description:

Subjects with symptomatic pulmonary arterial hypertension (PAH) who completed or have experienced a morbidity/clinical worsening of PAH in the study AC-055-302 and opted to continue this open label extension study received macitentan oral tablet, 10 milligram (mg) once daily from Day 1 up to end of study (Up to 12 years) which depends on following a). transition to commercially available macitentan in the subjects country b). the sponsor decided to stop the OL study, and c). the subjects or investigators or sponsors decision to discontinue study treatment

Reporting group title	Macitentan 10 mg		
Serious adverse events			
Total subjects affected by serious adverse events			
subjects affected / exposed	354 / 550 (64.36%)		
number of deaths (all causes)	175		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital Warts			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal Cell Carcinoma			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder Cancer			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Brain Neoplasm				
subjects affected / exposed	1 / 550 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac Valve Fibroelastoma				
subjects affected / exposed	1 / 550 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colon Cancer				
subjects affected / exposed	2 / 550 (0.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haemangioma				
subjects affected / exposed	1 / 550 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intraductal Proliferative Breast Lesion				
subjects affected / exposed	1 / 550 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Invasive Ductal Breast Carcinoma				
subjects affected / exposed	2 / 550 (0.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metastases to Lung				
subjects affected / exposed	2 / 550 (0.36%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
Metastatic Uterine Cancer				
subjects affected / exposed	1 / 550 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nasopharyngeal Cancer				

subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian Adenoma			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian Cancer			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Rectosigmoid Cancer Recurrent			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Richter's Syndrome			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Squamous Cell Carcinoma of Lung			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous Cell Carcinoma of the Cervix			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine Cancer			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine Leiomyoma			

subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Accelerated Hypertension			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aneurysm Ruptured			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Aortic Aneurysm			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aortic Aneurysm Rupture			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Circulatory Collapse			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Deep Vein Thrombosis			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haematoma			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			

subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	3 / 550 (0.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hypovolaemic Shock			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Venous Thrombosis Limb			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Aortic Surgery			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bunion Operation			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chemotherapy			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cholecystectomy			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric Polypectomy			

subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hysterectomy			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung Transplant			
subjects affected / exposed	7 / 550 (1.27%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 1		
Oophorectomy			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteosynthesis			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Therapy Cessation			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transfusion			
subjects affected / exposed	1 / 550 (0.18%)		
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 / 550 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abortion Spontaneous			

subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pregnancy			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Cardiac Death			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Chest Discomfort			
subjects affected / exposed	3 / 550 (0.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Chest Pain			
subjects affected / exposed	11 / 550 (2.00%)		
occurrences causally related to treatment / all	1 / 11		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	5 / 550 (0.91%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 5		
Drug Ineffective			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
General Physical Health Deterioration			

subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza Like Illness			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion Site Pain			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple Organ Dysfunction Syndrome			
subjects affected / exposed	4 / 550 (0.73%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		
Oedema Peripheral			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Peripheral Swelling			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	4 / 550 (0.73%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Sudden Cardiac Death			
subjects affected / exposed	3 / 550 (0.55%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 3		
Sudden Death			

subjects affected / exposed	11 / 550 (2.00%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 11		
Vascular Stent Thrombosis			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Menometrorrhagia			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Menorrhagia			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 0		
Metrorrhagia			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Ovarian Cyst			
subjects affected / exposed	4 / 550 (0.73%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

Ovarian Cyst Ruptured			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian Cyst Torsion			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic Haematoma			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostatitis			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine Haemorrhage			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vaginal Haemorrhage			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute Pulmonary Oedema			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Acute Respiratory Failure			
subjects affected / exposed	4 / 550 (0.73%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		

Asthma				
subjects affected / exposed	1 / 550 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis Chronic				
subjects affected / exposed	1 / 550 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchospasm				
subjects affected / exposed	1 / 550 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic Obstructive Pulmonary Disease				
subjects affected / exposed	1 / 550 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic Respiratory Failure				
subjects affected / exposed	1 / 550 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Dyspnoea				
subjects affected / exposed	16 / 550 (2.91%)			
occurrences causally related to treatment / all	2 / 17			
deaths causally related to treatment / all	0 / 1			
Dyspnoea Exertional				
subjects affected / exposed	5 / 550 (0.91%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	2 / 550 (0.36%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				

subjects affected / exposed	8 / 550 (1.45%)		
occurrences causally related to treatment / all	1 / 12		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	3 / 550 (0.55%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Nasal Polyps			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Organising Pneumonia			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural Effusion			
subjects affected / exposed	3 / 550 (0.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pulmonary Arterial Hypertension			
subjects affected / exposed	123 / 550 (22.36%)		
occurrences causally related to treatment / all	7 / 169		
deaths causally related to treatment / all	3 / 60		
Pulmonary Congestion			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary Embolism			
subjects affected / exposed	10 / 550 (1.82%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 7		
Pulmonary Fibrosis			

subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary Haemorrhage			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary Hypertension			
subjects affected / exposed	6 / 550 (1.09%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 1		
Pulmonary Hypertensive Crisis			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Pulmonary Oedema			
subjects affected / exposed	3 / 550 (0.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Respiratory Failure			
subjects affected / exposed	5 / 550 (0.91%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 2		
Respiratory Tract Haemorrhage			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anxiety Disorder			

subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Completed Suicide			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Confusional State			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mental Status Changes			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device Dislocation			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Device Malfunction			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Anticoagulation Drug Level above Therapeutic			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Blood Bilirubin Increased			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Catheterisation Cardiac			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Computerised Tomogram Abnormal			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
International Normalised Ratio Increased			
subjects affected / exposed	3 / 550 (0.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Investigation			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Liver Function Test Increased			
subjects affected / exposed	3 / 550 (0.55%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Oxygen Saturation Decreased			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Acetabulum Fracture				
subjects affected / exposed	1 / 550 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ankle Fracture				
subjects affected / exposed	1 / 550 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Brain Contusion				
subjects affected / exposed	1 / 550 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Contusion				
subjects affected / exposed	1 / 550 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	5 / 550 (0.91%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Femoral Neck Fracture				
subjects affected / exposed	1 / 550 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femur Fracture				
subjects affected / exposed	2 / 550 (0.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Foot Fracture				
subjects affected / exposed	1 / 550 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Humerus Fracture				

subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Perineal Injury			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post Procedural Haematoma			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post Procedural Haemorrhage			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Radius Fracture			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal Compression Fracture			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subarachnoid Haemorrhage			
subjects affected / exposed	3 / 550 (0.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Subdural Haematoma			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Thermal Burn			

subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thoracic Vertebral Fracture			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Toxicity to Various Agents			
subjects affected / exposed	3 / 550 (0.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Traumatic Haematoma			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Traumatic Haemorrhage			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ulna Fracture			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper Limb Fracture			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute Myocardial Infarction			

subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Acute Right Ventricular Failure			
subjects affected / exposed	11 / 550 (2.00%)		
occurrences causally related to treatment / all	1 / 11		
deaths causally related to treatment / all	0 / 7		
Angina Pectoris			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arrhythmia			
subjects affected / exposed	3 / 550 (0.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Atrial Fibrillation			
subjects affected / exposed	7 / 550 (1.27%)		
occurrences causally related to treatment / all	1 / 8		
deaths causally related to treatment / all	0 / 0		
Atrial Flutter			
subjects affected / exposed	8 / 550 (1.45%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac Arrest			
subjects affected / exposed	9 / 550 (1.64%)		
occurrences causally related to treatment / all	1 / 9		
deaths causally related to treatment / all	1 / 8		
Cardiac Disorder			

subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac Failure			
subjects affected / exposed	7 / 550 (1.27%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 4		
Cardiac Failure Acute			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac Failure Chronic			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac Failure Congestive			
subjects affected / exposed	6 / 550 (1.09%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 1		
Cardio-Respiratory Arrest			
subjects affected / exposed	4 / 550 (0.73%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 4		
Cardiogenic Shock			
subjects affected / exposed	9 / 550 (1.64%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 5		
Cardiopulmonary Failure			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Cardiorenal Syndrome			

subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic Right Ventricular Failure			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Coronary Artery Disease			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cyanosis			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Left Ventricular Dysfunction			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Left Ventricular Failure			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Myocardial Infarction			
subjects affected / exposed	4 / 550 (0.73%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Myocardial Ischaemia			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Palpitations			

subjects affected / exposed	3 / 550 (0.55%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Pericardial Effusion			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Right Ventricular Dysfunction			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Right Ventricular Failure			
subjects affected / exposed	72 / 550 (13.09%)		
occurrences causally related to treatment / all	1 / 108		
deaths causally related to treatment / all	0 / 35		
Stress Cardiomyopathy			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Supraventricular Tachycardia			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Tachyarrhythmia			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular Fibrillation			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Ventricular Tachycardia			

subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain Oedema			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cerebellar Infarction			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular Accident			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Dizziness			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatic Encephalopathy			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic Stroke			

subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Loss of Consciousness			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Polyneuropathy			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Radiculopathy			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	20 / 550 (3.64%)		
occurrences causally related to treatment / all	0 / 25		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	27 / 550 (4.91%)		
occurrences causally related to treatment / all	4 / 45		
deaths causally related to treatment / all	0 / 0		
Autoimmune Haemolytic Anaemia			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coagulopathy			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypercoagulation			

subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Iron Deficiency Anaemia			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	3 / 550 (0.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo Positional			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal Pain			
subjects affected / exposed	3 / 550 (0.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Abdominal Pain Upper			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Anal Fistula				
subjects affected / exposed	1 / 550 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 550 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	2 / 550 (0.36%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	3 / 550 (0.55%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Duodenal Perforation				
subjects affected / exposed	1 / 550 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis Haemorrhagic				
subjects affected / exposed	1 / 550 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	2 / 550 (0.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastritis Erosive				
subjects affected / exposed	1 / 550 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroduodenitis				

subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal Disorder			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal Haemorrhage			
subjects affected / exposed	3 / 550 (0.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Gastrointestinal Necrosis			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hiatus Hernia			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus Paralytic			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Intestinal Pseudo-Obstruction			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower Gastrointestinal Haemorrhage			

subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis Acute			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pancreatitis Relapsing			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Peptic Ulcer			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal Haemorrhage			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small Intestinal Obstruction			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Umbilical Hernia			
subjects affected / exposed	3 / 550 (0.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	6 / 550 (1.09%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 1		
Vomiting			

subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile Duct Stone			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis Acute			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic Function Abnormal			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatic Steatosis			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Photosensitivity Reaction			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rash Pruritic			

subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	8 / 550 (1.45%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 1		
Calculus Urinary			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic Kidney Disease			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis Haemorrhagic			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lupus Nephritis			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neurogenic Bladder			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pollakiuria			

subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prerenal Failure			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal Colic			
subjects affected / exposed	3 / 550 (0.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Renal Failure			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal Impairment			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ureterolithiasis			
subjects affected / exposed	1 / 550 (0.18%)		
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 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intervertebral Disc Degeneration			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral Disc Protrusion			

subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint Swelling			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mixed Connective Tissue Disease			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular Weakness			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal Pain			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoporosis			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in Extremity			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Polymyositis			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rheumatoid Arthritis			

subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Scleroderma			
subjects affected / exposed	3 / 550 (0.55%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Spinal Column Stenosis			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Systemic Lupus Erythematosus			
subjects affected / exposed	5 / 550 (0.91%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 1		
Systemic Scleroderma			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Infections and infestations			
Abscess Limb			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	3 / 550 (0.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Arthritis Bacterial			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atypical Pneumonia			

subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	9 / 550 (1.64%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Bronchitis Viral			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Candida Sepsis			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	4 / 550 (0.73%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Device Related Infection			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocarditis			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			

subjects affected / exposed	4 / 550 (0.73%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis Bacterial			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis Norovirus			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis Salmonella			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes Zoster			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hiv Infection			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Infected Skin Ulcer			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infective Exacerbation of Chronic Obstructive Airways Disease			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Influenza			

subjects affected / exposed	5 / 550 (0.91%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Joint Tuberculosis			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Laryngitis Bacterial			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Localised Infection			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower Respiratory Tract Infection			
subjects affected / exposed	8 / 550 (1.45%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Lung Infection			
subjects affected / exposed	8 / 550 (1.45%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 3		
Meningitis			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumococcal Sepsis			

subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	40 / 550 (7.27%)		
occurrences causally related to treatment / all	0 / 52		
deaths causally related to treatment / all	0 / 4		
Pneumonia Influenzal			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia Klebsiella			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia Streptococcal			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postoperative Wound Infection			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary Sepsis			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary Tuberculosis			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			

subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis Acute			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory Tract Infection			
subjects affected / exposed	3 / 550 (0.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory Tract Infection Viral			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Salmonella Sepsis			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	4 / 550 (0.73%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
Septic Shock			
subjects affected / exposed	6 / 550 (1.09%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 2		
Staphylococcal Bacteraemia			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subcutaneous Abscess			

subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Tuberculosis			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Upper Respiratory Tract Infection			
subjects affected / exposed	9 / 550 (1.64%)		
occurrences causally related to treatment / all	1 / 10		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Infection			
subjects affected / exposed	3 / 550 (0.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	4 / 550 (0.73%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Electrolyte Imbalance			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Fluid Overload			

subjects affected / exposed	4 / 550 (0.73%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 2		
Fluid Retention			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gout			
subjects affected / exposed	2 / 550 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	4 / 550 (0.73%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	5 / 550 (0.91%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 1		
Metabolic Acidosis			
subjects affected / exposed	1 / 550 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Macitentan 10 mg		
Total subjects affected by non-serious adverse events subjects affected / exposed	430 / 550 (78.18%)		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	34 / 550 (6.18%) 36		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Syncope subjects affected / exposed occurrences (all)	55 / 550 (10.00%) 73 63 / 550 (11.45%) 94 40 / 550 (7.27%) 64		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	80 / 550 (14.55%) 96 36 / 550 (6.55%) 42		
General disorders and administration site conditions Chest Pain subjects affected / exposed occurrences (all) Oedema Peripheral subjects affected / exposed occurrences (all)	35 / 550 (6.36%) 42 105 / 550 (19.09%) 143		
Gastrointestinal disorders Diarrhoea			

<p>subjects affected / exposed occurrences (all)</p> <p>Nausea subjects affected / exposed occurrences (all)</p>	<p>59 / 550 (10.73%) 85</p> <p>28 / 550 (5.09%) 32</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough subjects affected / exposed occurrences (all)</p> <p>Dyspnoea subjects affected / exposed occurrences (all)</p> <p>Pulmonary Arterial Hypertension subjects affected / exposed occurrences (all)</p>	<p>74 / 550 (13.45%) 89</p> <p>54 / 550 (9.82%) 65</p> <p>47 / 550 (8.55%) 51</p>		
<p>Psychiatric disorders</p> <p>Insomnia subjects affected / exposed occurrences (all)</p>	<p>36 / 550 (6.55%) 45</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia subjects affected / exposed occurrences (all)</p> <p>Back Pain subjects affected / exposed occurrences (all)</p>	<p>33 / 550 (6.00%) 38</p> <p>33 / 550 (6.00%) 34</p>		
<p>Infections and infestations</p> <p>Bronchitis subjects affected / exposed occurrences (all)</p> <p>Nasopharyngitis subjects affected / exposed occurrences (all)</p> <p>Pharyngitis subjects affected / exposed occurrences (all)</p>	<p>78 / 550 (14.18%) 126</p> <p>105 / 550 (19.09%) 203</p> <p>28 / 550 (5.09%) 48</p>		

Pneumonia subjects affected / exposed occurrences (all)	29 / 550 (5.27%) 34		
Respiratory Tract Infection subjects affected / exposed occurrences (all)	31 / 550 (5.64%) 49		
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	121 / 550 (22.00%) 310		
Urinary Tract Infection subjects affected / exposed occurrences (all)	46 / 550 (8.36%) 69		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	39 / 550 (7.09%) 59		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 July 2008	This amendment dated 18 July 2008 (Protocol Version 3) was considered substantial and included the following changes: added CYP3A4 inducers to the list of prohibited concomitant medications; added definitions of certain serious adverse events (SAEs)(expected in a PAH population) which did not require immediate reporting to Actelion Global Drug Safety on an SAE form unless the event was fatal.
22 September 2009	This amendment dated 22 September 2009 (Protocol Version 4) was considered substantial and included the following changes: increase the sample size from 525 to 699 subjects in the OL study due to the higher than expected enrolment in the OL study; change biweekly follow-up of subjects with elevated liver transaminases to weekly monitoring based on a request from the DSMB; implemented minor editorial changes.
27 August 2013	This amendment dated 27 August 2013 (Protocol Version 5) was considered substantial and included the following changes: all concomitant medications taken by a subject during the study were to be collected in the CRF to facilitate the evaluation of the safety and tolerability data; a central laboratory was to be used for prospective biochemistry and hematology analyses in accordance with the then draft FDA "Guidance for Industry Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations" (February 2012); a Independent Liver Safety Board was established to monitor the liver safety of macitentan including reviewing cases of confirmed elevations of aminotransferases >3x ULN during the study.
10 June 2016	This amendment dated 10 June 2016 (Protocol Version 6) was considered substantial and included the following changes: the requirement for mandatory monthly liver function tests (LFTs) was changed to recommended monthly LFTs, that is, LFTs were to be performed at the investigator's discretion as clinically indicated; this was based considering safety data from available macitentan exposure data; re-introduction of study treatment after absence of pregnancy was confirmed as study participation was the only option for subjects to continue receiving macitentan; following completion of enrollment into the study, the number of subjects included in the study was adjusted; align the concomitant medication section with the most current Investigator's Brochure (IB) to include the most up to date information on drug-drug interaction potential of macitentan; update drug storage and dispensing due to a change in the packaging of study treatment; update information regarding the reporting requirements of suspected SAEs in accordance with the EU guidance 2011/C 172/01: Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (CT-3).
17 July 2020	This amendment dated 17 July 2020 (Protocol Version 7) was considered substantial and included the following changes: to update the concomitant therapy section pertaining to newly identified drug-drug interactions (DDI) between macitentan and fluconazole (a dual moderate inhibitor of CYP3A4 and CYP2C9) from a preclinical study on implications of role of CYP2C9 in the metabolism of macitentan.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported