



Clinical trial results:

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Pulmaquin® in the Management of Chronic Lung Infections with Pseudomonas aeruginosa in Subjects with Non-Cystic Fibrosis Bronchiectasis, including 28 Day Open-Label Extension and Pharmacokinetic Substudy (ORBIT-3)

Summary

EudraCT number	2013-005348-28
Trial protocol	GB HU IT ES LV RO IE PL
Global end of trial date	14 October 2016

Results information

Result version number	v1 (current)
This version publication date	25 April 2018
First version publication date	25 April 2018

Trial information

Trial identification

Sponsor protocol code	ARD-3150-1201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01515007
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aradigm Corporation
Sponsor organisation address	3929 Point Eden Way, Hayward, California, United States, 94545
Public contact	Clinical Operations, Aradigm Corporation, +1 510 265 8895, JacksonA@aradigm.com
Scientific contact	Medical and Drug Development, Aradigm Corporation, +1 510 265 8838, froehlichj@aradigm.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	21 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 August 2016
Global end of trial reached?	Yes
Global end of trial date	14 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the efficacy of Linhaliq compared to placebo in the management of chronic lung infections with *P. aeruginosa* in subjects with non-cystic fibrosis (non-CF) bronchiectasis by evaluating the time to first pulmonary exacerbation in the Double-Blind Phase.

Protection of trial subjects:

The study was designed and monitored in accordance with Sponsor procedures, which comply with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 March 2014
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	Poland: 6
Country: Number of subjects enrolled	Romania: 14
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Latvia: 9
Country: Number of subjects enrolled	United States: 52
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Israel: 23
Country: Number of subjects enrolled	Australia: 70
Country: Number of subjects enrolled	South Africa: 14
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	Korea, Republic of: 2
Worldwide total number of subjects	278
EEA total number of subjects	101

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)	109
From 65 to 84 years	165
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

102 clinical sites screened at least one subject for the study. Sites were located in Australia, Canada, Germany, Hungary, Ireland, Israel, Italy, Latvia, Poland, Romania, South Africa, South Korea, Spain, Taiwan, the United Kingdom (UK), and the US. The first subject was screened on 31 March 2014, and the final subject screened on 19 August 2015.

Pre-assignment

Screening details:

514 subjects were enrolled and screened. Subjects who met all eligibility criteria were randomized in a 2:1 ratio to receive once daily inhaled treatment with Pulmaquin or placebo.

Period 1

Period 1 title	Double-Blind Phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Active

Arm description:

Liquid mixture of liposome-encapsulated and unencapsulated ciprofloxacin

Arm type	Experimental
Investigational medicinal product name	Linhaliq
Investigational medicinal product code	ARD-3150
Other name	Pulmaquin
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

The administered dose was 189 mg (6 mL) of ciprofloxacin comprised of one vial of 135 mg (3mL) liposome-encapsulated ciprofloxacin dispersion and one vial of 54 mg (3mL) free ciprofloxacin solution given once daily by oral inhalation using a nebuliser; the dosing regimen was 6 cycles of 28 days on treatment, followed by 28 days off treatment.

Arm title	Placebo
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Arm description:

Liquid mixture of empty liposomes and normal saline

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

The administered dose was 6 mL placebo, comprised of one vial of 3 mL empty liposomes and one vial of 3 mL normal saline solution once daily by oral inhalation using a nebuliser; the dosing regimen was 6 cycles of 28 days on treatment, followed by 28 days off treatment.

Number of subjects in period 1	Active	Placebo
Started	183	95
Completed	142	77
Not completed	41	18
Adverse event, serious fatal	5	3
Physician decision	3	1
Consent withdrawn by subject	14	11
Per-Protocol Defined Pulmonary Exacerbation	1	-
Adverse event, non-fatal	11	-
Other	-	1
Lost to follow-up	3	1
Lack of efficacy	2	-
Protocol deviation	2	1

Baseline characteristics

Reporting groups

Reporting group title	Active
Reporting group description: Liquid mixture of liposome-encapsulated and unencapsulated ciprofloxacin	
Reporting group title	Placebo
Reporting group description: Liquid mixture of empty liposomes and normal saline	

Reporting group values	Active	Placebo	Total
Number of subjects	183	95	278
Age categorical Units: Subjects			

Age continuous Units: years median full range (min-max)	68.0 21 to 86	69 21 to 87	-
Gender categorical Units: Subjects			
Female	127	67	194
Male	56	28	84

End points

End points reporting groups

Reporting group title	Active
Reporting group description:	
Liquid mixture of liposome-encapsulated and unencapsulated ciprofloxacin	
Reporting group title	Placebo
Reporting group description:	
Liquid mixture of empty liposomes and normal saline	

Primary: Time to First Pulmonary Exacerbation

End point title	Time to First Pulmonary Exacerbation
End point description:	
Median time to first pulmonary exacerbation	
End point type	Primary
End point timeframe:	
March 2014 to August 2016	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	95		
Units: Number of days				
median (confidence interval 95%)	214.0 (114.0 to 289.0)	136.0 (81.0 to 339.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Active v Placebo
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9743
Method	Stratified Unweighted Log-Rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.38

Secondary: Frequency of Pulmonary Exacerbations

End point title	Frequency of Pulmonary Exacerbations
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End point description:

End point type	Secondary
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End point timeframe:

March 2014 to August 2016

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	95		
Units: Number of Pulmonary Exacerbations				
arithmetic mean (standard error)	1.09 (\pm 0.10)	1.31 (\pm 0.12)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Active v Placebo
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2565
Method	Stratified Negative Binomial Regression
Parameter estimate	Risk ratio (RR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.12

Statistical analysis title	Statistical Analysis 2
Comparison groups	Active v Placebo

Number of subjects included in analysis	278
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.136
Method	Counting Process
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.06

Secondary: Frequency of Moderate and Severe Pulmonary Exacerbations

End point title	Frequency of Moderate and Severe Pulmonary Exacerbations
End point description:	
End point type	Secondary
End point timeframe:	
March 2014 to August 2016	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	95		
Units: Number of Pulmonary Exacerbations				
arithmetic mean (standard error)	0.86 (± 0.10)	1.13 (± 0.13)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Active
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0998
Method	Stratified Negative Binomial Regression
Parameter estimate	Risk ratio (RR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.05

Statistical analysis title	Statistical Analysis 2
Comparison groups	Active v Placebo
Number of subjects included in analysis	278
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.038
Method	Counting Process
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	0.99

Secondary: Frequency of Severe Pulmonary Exacerbations

End point title	Frequency of Severe Pulmonary Exacerbations
End point description:	
End point type	Secondary
End point timeframe:	
March 2014 to August 2016	

End point values	Active	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	95		
Units: Number of Pulmonary Exacerbations				
arithmetic mean (standard error)	0.22 (± 0.22)	0.28 (± 0.28)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Active v Placebo

Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4827
Method	Stratified Negative Binomial Regression
Parameter estimate	Risk ratio (RR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.51

Statistical analysis title	Statistical Analysis 2
Comparison groups	Active v Placebo
Number of subjects included in analysis	278
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.399
Method	Counting Process
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.32

Adverse events

Adverse events information

Timeframe for reporting adverse events:

March 2014 to August 2016

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Active
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Reporting group description:

Liquid mixture of liposome-encapsulated and unencapsulated ciprofloxacin

Reporting group title	Placebo
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Reporting group description:

Liquid mixture of empty liposomes and normal saline

Serious adverse events	Active	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	56 / 183 (30.60%)	24 / 95 (25.26%)	
number of deaths (all causes)	5	3	
number of deaths resulting from adverse events	5	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granulomatosis with polyangiitis			

subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device failure			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 183 (0.00%)	2 / 95 (2.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 183 (0.55%)	3 / 95 (3.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vessel puncture site haematoma			

subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exercise tolerance decreased			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asphyxia			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asthma			
subjects affected / exposed	1 / 183 (0.55%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial secretion retention			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			

subjects affected / exposed	5 / 183 (2.73%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	11 / 183 (6.01%)	8 / 95 (8.42%)	
occurrences causally related to treatment / all	2 / 16	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	7 / 183 (3.83%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	1 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways disorder			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 183 (0.55%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	5 / 183 (2.73%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sputum increased			
subjects affected / exposed	1 / 183 (0.55%)	4 / 95 (4.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wheezing			
subjects affected / exposed	1 / 183 (0.55%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Breath sounds abnormal			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest X-ray abnormal			
subjects affected / exposed	1 / 183 (0.55%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibrin D dimer increased			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forced expiratory volume decreased			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Tendon rupture			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Left ventricle outflow tract obstruction			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 183 (0.55%)	2 / 95 (2.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 183 (0.00%)	2 / 95 (2.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			

subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thalamus haemorrhage			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Unresponsive to stimuli			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Nephrotic syndrome			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis perforated			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 183 (1.09%)	5 / 95 (5.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 183 (3.83%)	6 / 95 (6.32%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumonia bacterial			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sputum purulent			

subjects affected / exposed	1 / 183 (0.55%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Active	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	164 / 183 (89.62%)	87 / 95 (91.58%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	

Basal cell carcinoma			
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)	
occurrences (all)	2	0	
Craniopharyngioma			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Seborrhoeic keratosis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Squamous cell carcinoma of skin			
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)	
occurrences (all)	4	0	
Vascular neoplasm			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)	
occurrences (all)	2	0	
Granulomatosis with polyangiitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Haematoma			
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)	
occurrences (all)	2	0	
Hypertension			
subjects affected / exposed	3 / 183 (1.64%)	3 / 95 (3.16%)	
occurrences (all)	3	5	
Hypertensive crisis			
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)	
occurrences (all)	3	0	
Hypotension			
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)	
occurrences (all)	2	0	
Surgical and medical procedures			

Spinal laminectomy subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	8 / 183 (4.37%) 8	3 / 95 (3.16%) 3	
Chest discomfort subjects affected / exposed occurrences (all)	10 / 183 (5.46%) 10	3 / 95 (3.16%) 5	
Chest pain subjects affected / exposed occurrences (all)	11 / 183 (6.01%) 14	5 / 95 (5.26%) 5	
Chills subjects affected / exposed occurrences (all)	2 / 183 (1.09%) 2	0 / 95 (0.00%) 0	
Device dislocation subjects affected / exposed occurrences (all)	0 / 183 (0.00%) 0	1 / 95 (1.05%) 1	
Exercise tolerance decreased subjects affected / exposed occurrences (all)	43 / 183 (23.50%) 61	22 / 95 (23.16%) 38	
fatigue subjects affected / exposed occurrences (all)	71 / 183 (38.80%) 133	40 / 95 (42.11%) 79	
Feeling cold subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	
Gravitational oedema subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	
Hernia subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	
Injection site discomfort			

subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	16 / 183 (8.74%)	14 / 95 (14.74%)	
occurrences (all)	20	23	
Oedema			
subjects affected / exposed	2 / 183 (1.09%)	1 / 95 (1.05%)	
occurrences (all)	2	1	
Oedema peripheral			
subjects affected / exposed	7 / 183 (3.83%)	1 / 95 (1.05%)	
occurrences (all)	8	1	
Pain			
subjects affected / exposed	6 / 183 (3.28%)	1 / 95 (1.05%)	
occurrences (all)	6	1	
Peripheral swelling			
subjects affected / exposed	2 / 183 (1.09%)	2 / 95 (2.11%)	
occurrences (all)	2	2	
Product taste abnormal			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	47 / 183 (25.68%)	31 / 95 (32.63%)	
occurrences (all)	73	51	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Seasonal allergy			
subjects affected / exposed	4 / 183 (2.19%)	0 / 95 (0.00%)	
occurrences (all)	4	0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Breast mass			

subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Allergic sinusitis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Asthma			
subjects affected / exposed	2 / 183 (1.09%)	1 / 95 (1.05%)	
occurrences (all)	2	1	
Bronchial hyperreactivity			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Bronchial secretion retention			
subjects affected / exposed	1 / 183 (0.55%)	2 / 95 (2.11%)	
occurrences (all)	4	2	
Bronchospasm			
subjects affected / exposed	3 / 183 (1.64%)	1 / 95 (1.05%)	
occurrences (all)	4	1	
Catarrh			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Choking sensation			
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)	
occurrences (all)	2	0	
Cough			
subjects affected / exposed	113 / 183 (61.75%)	55 / 95 (57.89%)	
occurrences (all)	279	137	
Dysphonia			
subjects affected / exposed	3 / 183 (1.64%)	7 / 95 (7.37%)	
occurrences (all)	3	7	
Dyspnoea			

subjects affected / exposed	98 / 183 (53.55%)	45 / 95 (47.37%)
occurrences (all)	189	105
Dyspnoea exertional		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	2	0
Epistaxis		
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)
occurrences (all)	2	0
Haemoptysis		
subjects affected / exposed	27 / 183 (14.75%)	9 / 95 (9.47%)
occurrences (all)	43	9
Hypopnoea		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Hypoxia		
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)
occurrences (all)	2	0
Increased viscosity of bronchial secretion		
subjects affected / exposed	23 / 183 (12.57%)	12 / 95 (12.63%)
occurrences (all)	31	15
Lung infiltration		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Nasal congestion		
subjects affected / exposed	6 / 183 (3.28%)	4 / 95 (4.21%)
occurrences (all)	8	4
Obstructive airways disorder		
subjects affected / exposed	3 / 183 (1.64%)	0 / 95 (0.00%)
occurrences (all)	3	0
Oropharyngeal pain		
subjects affected / exposed	9 / 183 (4.92%)	7 / 95 (7.37%)
occurrences (all)	11	8
Paranasal sinus discomfort		
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)
occurrences (all)	2	0

Pharyngeal erythema		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Pharyngeal oedema		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Pleurisy		
subjects affected / exposed	4 / 183 (2.19%)	3 / 95 (3.16%)
occurrences (all)	6	5
Pleuritic pain		
subjects affected / exposed	3 / 183 (1.64%)	0 / 95 (0.00%)
occurrences (all)	3	0
Productive cough		
subjects affected / exposed	5 / 183 (2.73%)	0 / 95 (0.00%)
occurrences (all)	5	0
Prolonged expiration		
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)
occurrences (all)	2	0
Pulmonary mass		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Rales		
subjects affected / exposed	8 / 183 (4.37%)	2 / 95 (2.11%)
occurrences (all)	9	2
Respiratory failure		
subjects affected / exposed	0 / 183 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	2
Respiratory tract congestion		
subjects affected / exposed	7 / 183 (3.83%)	1 / 95 (1.05%)
occurrences (all)	8	4
Respiratory tract irritation		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Rhinitis allergic		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0

Rhinorrhoea		
subjects affected / exposed	3 / 183 (1.64%)	6 / 95 (6.32%)
occurrences (all)	3	6
Rhonchi		
subjects affected / exposed	6 / 183 (3.28%)	1 / 95 (1.05%)
occurrences (all)	9	1
Sinus congestion		
subjects affected / exposed	0 / 183 (0.00%)	4 / 95 (4.21%)
occurrences (all)	0	4
Sinus polyp		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Sleep apnoea syndrome		
subjects affected / exposed	1 / 183 (0.55%)	1 / 95 (1.05%)
occurrences (all)	1	1
Sputum decreased		
subjects affected / exposed	2 / 183 (1.09%)	1 / 95 (1.05%)
occurrences (all)	2	1
Sputum discoloured		
subjects affected / exposed	8 / 183 (4.37%)	4 / 95 (4.21%)
occurrences (all)	8	4
Sputum increased		
subjects affected / exposed	82 / 183 (44.81%)	43 / 95 (45.26%)
occurrences (all)	156	98
Sputum retention		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Throat irritation		
subjects affected / exposed	4 / 183 (2.19%)	2 / 95 (2.11%)
occurrences (all)	10	2
Upper-airway cough syndrome		
subjects affected / exposed	2 / 183 (1.09%)	1 / 95 (1.05%)
occurrences (all)	2	1
Wheezing		
subjects affected / exposed	69 / 183 (37.70%)	35 / 95 (36.84%)
occurrences (all)	129	70

Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Anxiety			
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)	
occurrences (all)	2	0	
Depressed mood			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	3 / 183 (1.64%)	3 / 95 (3.16%)	
occurrences (all)	3	3	
Disorientation			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	2 / 183 (1.09%)	4 / 95 (4.21%)	
occurrences (all)	2	4	
Major depression			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Mental status changes			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Nightmare			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Panic attack			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
dysthymic disorder			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Investigations			

Alanine aminotransferase increased		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Bacterial test positive		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Blood alkaline phosphatase increased		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Blood bilirubin increased		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Blood cholesterol increased		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Blood creatine phosphokinase increased		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Blood glucose increased		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Blood pressure increased		
subjects affected / exposed	1 / 183 (0.55%)	1 / 95 (1.05%)
occurrences (all)	1	1
Blood urine present		
subjects affected / exposed	3 / 183 (1.64%)	0 / 95 (0.00%)
occurrences (all)	3	0
Body temperature increased		
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)
occurrences (all)	2	0
Breath sounds abnormal		
subjects affected / exposed	42 / 183 (22.95%)	16 / 95 (16.84%)
occurrences (all)	54	23
Cardiac murmur		

subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)
occurrences (all)	2	0
Chest X-ray		
subjects affected / exposed	4 / 183 (2.19%)	3 / 95 (3.16%)
occurrences (all)	4	3
Fibrin D dimer increased		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Forced expiratory volume decreased		
subjects affected / exposed	62 / 183 (33.88%)	19 / 95 (20.00%)
occurrences (all)	86	25
Forced vital capacity decreased		
subjects affected / exposed	37 / 183 (20.22%)	14 / 95 (14.74%)
occurrences (all)	48	22
Heart rate increased		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Heart rate irregular		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	2	0
International normalised ratio increased		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Lymph node palpable		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Lymphocyte count increased		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Mean cell volume increased		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Monocyte count increased		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0

Neutrophil count increased subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 2	0 / 95 (0.00%) 0
Occult blood positive subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0
Oxygen saturation decreased subjects affected / exposed occurrences (all)	4 / 183 (2.19%) 7	0 / 95 (0.00%) 0
Protein urine present subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0
Pulmonary function test decreased subjects affected / exposed occurrences (all)	19 / 183 (10.38%) 33	11 / 95 (11.58%) 23
Spirometry abnormal subjects affected / exposed occurrences (all)	0 / 183 (0.00%) 0	1 / 95 (1.05%) 1
Sputum abnormal subjects affected / exposed occurrences (all)	22 / 183 (12.02%) 38	12 / 95 (12.63%) 25
Staphylococcus test positive subjects affected / exposed occurrences (all)	0 / 183 (0.00%) 0	1 / 95 (1.05%) 1
Urinary sediment present subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0
Weight decreased subjects affected / exposed occurrences (all)	4 / 183 (2.19%) 5	2 / 95 (2.11%) 2
Weight increased subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0
White blood cells urine positive subjects affected / exposed occurrences (all)	2 / 183 (1.09%) 3	0 / 95 (0.00%) 0

Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Arthropod bite			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Arthropod sting			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Chemical burn of skin			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Chest injury			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	2	0	
Contusion			
subjects affected / exposed	2 / 183 (1.09%)	5 / 95 (5.26%)	
occurrences (all)	4	7	
Epicondylitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Facial bones fracture			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	4 / 183 (2.19%)	2 / 95 (2.11%)	
occurrences (all)	4	3	
Head injury			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Incisional hernia			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Laceration			

subjects affected / exposed	3 / 183 (1.64%)	3 / 95 (3.16%)	
occurrences (all)	5	3	
Ligament sprain			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Limb injury			
subjects affected / exposed	2 / 183 (1.09%)	1 / 95 (1.05%)	
occurrences (all)	2	1	
Muscle strain			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Rib fracture			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Skin wound			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Soft tissue injury			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Thermal burn			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Tooth fracture			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 183 (0.55%)	1 / 95 (1.05%)	
occurrences (all)	1	1	
Atrial fibrillation			
subjects affected / exposed	3 / 183 (1.64%)	0 / 95 (0.00%)	
occurrences (all)	4	0	
Bradycardia			
subjects affected / exposed	3 / 183 (1.64%)	0 / 95 (0.00%)	
occurrences (all)	3	0	

Bundle branch block left			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Cardiac failure congestive			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Cardiomyopathy			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Cor pulmonale			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	0 / 183 (0.00%)	2 / 95 (2.11%)	
occurrences (all)	0	2	
Supraventricular extrasystoles			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	1 / 183 (0.55%)	1 / 95 (1.05%)	
occurrences (all)	1	1	
Nervous system disorders			
Anosmia			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Aphonia			
subjects affected / exposed	1 / 183 (0.55%)	1 / 95 (1.05%)	
occurrences (all)	2	1	
Autonomic nervous system imbalance			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Carpal tunnel syndrome			

subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Dizziness		
subjects affected / exposed	15 / 183 (8.20%)	5 / 95 (5.26%)
occurrences (all)	21	5
Dysarthria		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Dysgeusia		
subjects affected / exposed	19 / 183 (10.38%)	6 / 95 (6.32%)
occurrences (all)	48	7
Encephalopathy		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Headache		
subjects affected / exposed	21 / 183 (11.48%)	11 / 95 (11.58%)
occurrences (all)	35	12
Hemiparesis		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Hypersomnia		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Hypogeusia		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Hypoxic-ischaemic encephalopathy		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Lethargy		
subjects affected / exposed	39 / 183 (21.31%)	18 / 95 (18.95%)
occurrences (all)	61	29
Memory impairment		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Migraine		

subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	13	0	
Neuralgia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Polyneuropathy			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Poor quality sleep			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Restless legs syndrome			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	2	0	
Sciatica			
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)	
occurrences (all)	2	0	
Sinus headache			
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)	
occurrences (all)	3	0	
Tremor			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Vocal cord paralysis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 183 (2.73%)	0 / 95 (0.00%)	
occurrences (all)	5	0	
Iron deficiency anaemia			
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)	
occurrences (all)	2	0	
Leukocytosis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	

Lymphadenopathy subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 183 (0.00%) 0	1 / 95 (1.05%) 1	
Ear and labyrinth disorders			
Cerumen impaction subjects affected / exposed occurrences (all)	0 / 183 (0.00%) 0	1 / 95 (1.05%) 1	
Deafness neurosensory subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	
Ear congestion subjects affected / exposed occurrences (all)	0 / 183 (0.00%) 0	1 / 95 (1.05%) 2	
Ear discomfort subjects affected / exposed occurrences (all)	2 / 183 (1.09%) 2	0 / 95 (0.00%) 0	
Ear haemorrhage subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	
Ear pain subjects affected / exposed occurrences (all)	3 / 183 (1.64%) 4	0 / 95 (0.00%) 0	
Hypoacusis subjects affected / exposed occurrences (all)	2 / 183 (1.09%) 2	0 / 95 (0.00%) 0	
Middle ear effusion subjects affected / exposed occurrences (all)	0 / 183 (0.00%) 0	1 / 95 (1.05%) 2	
Motion sickness subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	
Otorrhoea			

subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	
Tinnitus subjects affected / exposed occurrences (all)	3 / 183 (1.64%) 3	1 / 95 (1.05%) 1	
Vertigo subjects affected / exposed occurrences (all)	3 / 183 (1.64%) 4	0 / 95 (0.00%) 0	
Eye disorders			
Cataract subjects affected / exposed occurrences (all)	2 / 183 (1.09%) 2	1 / 95 (1.05%) 1	
Conjunctival haemorrhage subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	
Conjunctivitis allergic subjects affected / exposed occurrences (all)	0 / 183 (0.00%) 0	1 / 95 (1.05%) 1	
Dacryostenosis acquired subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	
Dry eye subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	1 / 95 (1.05%) 1	
Eye pain subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	
Macular degeneration subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	
Ocular discomfort subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	
Ocular hypertension subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	

Uveitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Xerophthalmia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	2	0	
Abdominal pain			
subjects affected / exposed	8 / 183 (4.37%)	0 / 95 (0.00%)	
occurrences (all)	9	0	
Abdominal pain upper			
subjects affected / exposed	3 / 183 (1.64%)	0 / 95 (0.00%)	
occurrences (all)	3	0	
Change of bowel habit			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Coating in mouth			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	5 / 183 (2.73%)	3 / 95 (3.16%)	
occurrences (all)	5	3	
Diarrhoea			
subjects affected / exposed	7 / 183 (3.83%)	9 / 95 (9.47%)	
occurrences (all)	8	11	
Diverticulum			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Dry mouth			
subjects affected / exposed	3 / 183 (1.64%)	2 / 95 (2.11%)	
occurrences (all)	4	2	
Dyspepsia			

subjects affected / exposed	2 / 183 (1.09%)	1 / 95 (1.05%)
occurrences (all)	2	1
Dysphagia		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Faecaloma		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Flatulence		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Frequent bowel movements		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Gastric ulcer		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Gastrooesophageal reflux disease		
subjects affected / exposed	1 / 183 (0.55%)	3 / 95 (3.16%)
occurrences (all)	1	3
Haemorrhoidal haemorrhage		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Haemorrhoids		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Hiatus hernia		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Hypoaesthesia oral		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Inguinal hernia		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Irritable bowel syndrome		

subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Lip swelling		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Mouth ulceration		
subjects affected / exposed	1 / 183 (0.55%)	2 / 95 (2.11%)
occurrences (all)	2	2
Nausea		
subjects affected / exposed	16 / 183 (8.74%)	4 / 95 (4.21%)
occurrences (all)	24	4
Rectal haemorrhage		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Retching		
subjects affected / exposed	3 / 183 (1.64%)	0 / 95 (0.00%)
occurrences (all)	5	0
Stomatitis		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Swollen tongue		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Tongue discolouration		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Tongue disorder		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Tongue eruption		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Toothache		
subjects affected / exposed	1 / 183 (0.55%)	1 / 95 (1.05%)
occurrences (all)	1	1
Vomiting		

subjects affected / exposed occurrences (all)	9 / 183 (4.92%) 9	3 / 95 (3.16%) 3	
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Jaundice			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Actinic keratosis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Blister rupture			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Decubitus ulcer			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Dermal cyst			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Dermatitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Dermatitis allergic			
subjects affected / exposed	0 / 183 (0.00%)	2 / 95 (2.11%)	
occurrences (all)	0	2	
Dry skin			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Eczema			

subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Erythema		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Hyperhidrosis		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Macule		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Miliaria		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Nail bed inflammation		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Pruritus		
subjects affected / exposed	6 / 183 (3.28%)	1 / 95 (1.05%)
occurrences (all)	7	1
Rash		
subjects affected / exposed	6 / 183 (3.28%)	2 / 95 (2.11%)
occurrences (all)	8	2
Rash erythematous		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Rash papular		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Skin lesion		
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)
occurrences (all)	3	0
Urticaria		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Vasculitic rash		

subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 183 (1.64%)	1 / 95 (1.05%)	
occurrences (all)	3	1	
Dysuria			
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)	
occurrences (all)	2	0	
Haematuria			
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)	
occurrences (all)	4	0	
Nephrolithiasis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Nephrotic syndrome			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Nocturia			
subjects affected / exposed	1 / 183 (0.55%)	1 / 95 (1.05%)	
occurrences (all)	1	1	
Pollakiuria			
subjects affected / exposed	1 / 183 (0.55%)	1 / 95 (1.05%)	
occurrences (all)	1	1	
Renal cyst			
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)	
occurrences (all)	2	0	
Urinary incontinence			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Hyperparathyroidism secondary			

subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Hyperthyroidism			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 183 (5.46%)	4 / 95 (4.21%)	
occurrences (all)	12	4	
Arthritis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	2	0	
Arthritis reactive			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	13 / 183 (7.10%)	3 / 95 (3.16%)	
occurrences (all)	16	4	
Groin pain			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Joint range of motion decreased			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	2	0	
Limb discomfort			
subjects affected / exposed	2 / 183 (1.09%)	1 / 95 (1.05%)	
occurrences (all)	2	1	
Muscle spasms			
subjects affected / exposed	3 / 183 (1.64%)	2 / 95 (2.11%)	
occurrences (all)	4	2	
Muscular weakness			
subjects affected / exposed	3 / 183 (1.64%)	0 / 95 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal chest pain			

subjects affected / exposed	3 / 183 (1.64%)	2 / 95 (2.11%)
occurrences (all)	3	2
Musculoskeletal discomfort		
subjects affected / exposed	0 / 183 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	2
Musculoskeletal pain		
subjects affected / exposed	3 / 183 (1.64%)	3 / 95 (3.16%)
occurrences (all)	4	3
Myalgia		
subjects affected / exposed	5 / 183 (2.73%)	2 / 95 (2.11%)
occurrences (all)	7	2
Neck pain		
subjects affected / exposed	2 / 183 (1.09%)	1 / 95 (1.05%)
occurrences (all)	2	1
Osteoarthritis		
subjects affected / exposed	1 / 183 (0.55%)	1 / 95 (1.05%)
occurrences (all)	1	2
Osteopenia		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Osteoporosis		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Pain in extremity		
subjects affected / exposed	11 / 183 (6.01%)	1 / 95 (1.05%)
occurrences (all)	13	1
Polymyalgia rheumatica		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Rhabdomyolysis		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Rotator cuff syndrome		
subjects affected / exposed	1 / 183 (0.55%)	2 / 95 (2.11%)
occurrences (all)	2	2
Soft tissue mass		

subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Spinal column stenosis			
subjects affected / exposed	1 / 183 (0.55%)	1 / 95 (1.05%)	
occurrences (all)	1	1	
Spinal osteoarthritis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Tendonitis			
subjects affected / exposed	2 / 183 (1.09%)	1 / 95 (1.05%)	
occurrences (all)	3	1	
Tenosynovitis stenosans			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Acute sinusitis			
subjects affected / exposed	2 / 183 (1.09%)	1 / 95 (1.05%)	
occurrences (all)	2	1	
Bacterial disease carrier			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Bacterial vaginosis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	3 / 183 (1.64%)	1 / 95 (1.05%)	
occurrences (all)	5	1	
Candida infection			
subjects affected / exposed	1 / 183 (0.55%)	1 / 95 (1.05%)	
occurrences (all)	1	2	
Cellulitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	

Corneal infection		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Cystitis		
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)
occurrences (all)	3	0
Ear infection		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Eye infection		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Fungal infection		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Gastroenteritis		
subjects affected / exposed	1 / 183 (0.55%)	1 / 95 (1.05%)
occurrences (all)	1	1
Gastrointestinal infection		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	2	0
Gingival abscess		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Haemophilus infection		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	2
Helicobacter infection		
subjects affected / exposed	2 / 183 (1.09%)	1 / 95 (1.05%)
occurrences (all)	2	2
Herpes simplex		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Herpes zoster		
subjects affected / exposed	1 / 183 (0.55%)	1 / 95 (1.05%)
occurrences (all)	1	1

Impetigo		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Infected cyst		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Influenza		
subjects affected / exposed	4 / 183 (2.19%)	3 / 95 (3.16%)
occurrences (all)	4	3
Laryngitis		
subjects affected / exposed	2 / 183 (1.09%)	1 / 95 (1.05%)
occurrences (all)	2	2
Localised infection		
subjects affected / exposed	3 / 183 (1.64%)	1 / 95 (1.05%)
occurrences (all)	3	1
Lower respiratory tract infection		
subjects affected / exposed	5 / 183 (2.73%)	4 / 95 (4.21%)
occurrences (all)	7	7
Lung infection		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Nasopharyngitis		
subjects affected / exposed	8 / 183 (4.37%)	5 / 95 (5.26%)
occurrences (all)	11	5
Onychomycosis		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Ophthalmic herpes zoster		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Oral candidiasis		
subjects affected / exposed	6 / 183 (3.28%)	1 / 95 (1.05%)
occurrences (all)	7	1
Oral herpes		
subjects affected / exposed	3 / 183 (1.64%)	2 / 95 (2.11%)
occurrences (all)	3	2

Oropharyngeal candidiasis		
subjects affected / exposed	0 / 183 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	2
Otitis media		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Peritonitis		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Pharyngitis		
subjects affected / exposed	1 / 183 (0.55%)	2 / 95 (2.11%)
occurrences (all)	1	2
Pneumonia		
subjects affected / exposed	6 / 183 (3.28%)	3 / 95 (3.16%)
occurrences (all)	6	3
Pseudomonas infection		
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)
occurrences (all)	2	0
Respiratory tract infection		
subjects affected / exposed	2 / 183 (1.09%)	0 / 95 (0.00%)
occurrences (all)	3	0
Respiratory tract infection viral		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Rhinitis		
subjects affected / exposed	5 / 183 (2.73%)	3 / 95 (3.16%)
occurrences (all)	7	3
Sepsis		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Septic shock		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Sialoadenitis		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0

Sinobronchitis		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Sinusitis		
subjects affected / exposed	4 / 183 (2.19%)	5 / 95 (5.26%)
occurrences (all)	5	8
Sputum purulent		
subjects affected / exposed	34 / 183 (18.58%)	13 / 95 (13.68%)
occurrences (all)	54	19
Tooth abscess		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Tooth infection		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Tracheitis		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0
Upper respiratory tract infection		
subjects affected / exposed	9 / 183 (4.92%)	1 / 95 (1.05%)
occurrences (all)	13	1
Urinary tract infection		
subjects affected / exposed	9 / 183 (4.92%)	2 / 95 (2.11%)
occurrences (all)	10	2
Vestibular neuronitis		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Viral infection		
subjects affected / exposed	0 / 183 (0.00%)	2 / 95 (2.11%)
occurrences (all)	0	2
Viral pharyngitis		
subjects affected / exposed	0 / 183 (0.00%)	1 / 95 (1.05%)
occurrences (all)	0	1
Vulvovaginal candidiasis		
subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)
occurrences (all)	1	0

Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	
Wound infection subjects affected / exposed occurrences (all)	0 / 183 (0.00%) 0	1 / 95 (1.05%) 1	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	2 / 183 (1.09%) 3	1 / 95 (1.05%) 1	
Dehydration subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	
Gout subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	
Hyperlipidaemia subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	
Hypomagnesaemia subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	1 / 95 (1.05%) 1	
Hyponatraemia subjects affected / exposed occurrences (all)	3 / 183 (1.64%) 3	1 / 95 (1.05%) 1	
Hypovolaemia subjects affected / exposed occurrences (all)	2 / 183 (1.09%) 2	0 / 95 (0.00%) 0	
Iron deficiency subjects affected / exposed occurrences (all)	1 / 183 (0.55%) 1	0 / 95 (0.00%) 0	
Lactose intolerance			

subjects affected / exposed	1 / 183 (0.55%)	0 / 95 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported