Clinical trial results:
A randomised, double-blind, double dummy, 56 week placebo-controlled, multicentre, parallel group, phase 3 study evaluating efficacy/safety of 3 benralizumab doses in patients with moderate to very severe COPD with previous exacerbations.

Summary

EudraCT number	2013-004579-11
Trial protocol	DK SE BE PL BG FR SI HR
Global end of trial date	09 April 2018

Results information

Result version number	v1 (current)
This version publication date	03 April 2019
First version publication date	03 April 2019

Trial information

Trial identification

Sponsor protocol code	D3251C00004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02155660
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Vastra Malarehamnen 9, So dertalje, Sweden, 151 85
Public contact	Ulbaldo Martin, AstraZeneca AB, ulbaldo.martin@astrazeneca.com
Scientific contact	AstraZeneca Clinical Study Information, AstraZeneca AB, information.center@astrazeneca.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	09 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 April 2018
Global end of trial reached?	Yes
Global end of trial date	09 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to determine if benralizumab reduces COPD exacerbation rate in symptomatic patients with moderate to very severe COPD who are receiving standard of care therapies.

Protection of trial subjects:

The Independent Data Monitoring Committee is responsible for monitoring the safety of the study participants, ensuring that the studies are being conducted with the highest scientific and ethical standards and making appropriate recommendations based on the available data. The IDMC functions independently of all other individuals associated with the conduct of the studies, including the study sponsor AstraZeneca. The committee is operated in accordance with an Independent Data Monitoring Committee Charter.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 June 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	Argentina: 282
Country: Number of subjects enrolled	Australia: 24
Country: Number of subjects enrolled	Belgium: 37
Country: Number of subjects enrolled	Brazil: 99
Country: Number of subjects enrolled	Bulgaria: 125
Country: Number of subjects enrolled	Chile: 42
Country: Number of subjects enrolled	Colombia: 54
Country: Number of subjects enrolled	Croatia: 3
Country: Number of subjects enrolled	Denmark: 73
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Israel: 49
Country: Number of subjects enrolled	Mexico: 37
Country: Number of subjects enrolled	New Zealand: 25
Country: Number of subjects enrolled	Norway: 21
Country: Number of subjects enrolled	Peru: 69
Country: Number of subjects enrolled	Philippines: 143
Country: Number of subjects enrolled	Poland: 191
Country: Number of subjects enrolled	Serbia: 3

Country: Number of subjects enrolled	Slovenia: 12
Country: Number of subjects enrolled	Sweden: 33
Country: Number of subjects enrolled	Taiwan: 25
Country: Number of subjects enrolled	Thailand: 27
Country: Number of subjects enrolled	Turkey: 50
Country: Number of subjects enrolled	Ukraine: 178
Country: Number of subjects enrolled	United States: 561
Country: Number of subjects enrolled	Vietnam: 61
Worldwide total number of subjects	2254
EEA total number of subjects	525

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)	1040
From 65 to 84 years	1210
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

6059 participants signed informed consent form, 2254 participants were randomised to receive treatment with benralizumab 10 mg, 30 mg, 100 mg, or placebo. All randomised participants were treated.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Benralizumab 10 mg

Arm description:

Every 8 weeks administered subcutaneously

Arm type	Experimental
Investigational medicinal product name	Benralizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

10 mg

Arm title	Benralizumab 30 mg

Arm description:

Every 8 weeks administered subcutaneously

Arm type	Experimental
Investigational medicinal product name	Benralizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

30 mg

Arm title	Benralizumab 100 mg

Arm description:

Every 8 weeks administered subcutaneously

Arm type	Experimental
Investigational medicinal product name	Benralizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:
100 mg

Arm title	Placebo

Arm description:
Every 8 weeks administered subcutaneously

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:
0 mg (matching placebo dose)

Number of subjects in period 1	Benralizumab 10 mg	Benralizumab 30 mg	Benralizumab 100 mg
Started	562	562	562
Completed	504	489	502
Not completed	58	73	60
Adverse event, serious fatal	17	19	17
Consent withdrawn by subject	28	31	24
Adverse event, non-fatal	2	6	3
Other Reason	8	6	10
Study-specific withdrawal criteria	-	1	1
Lost to follow-up	3	6	5
Severe non-compliance	-	4	-

Number of subjects in period 1	Placebo
Started	568
Completed	507
Not completed	61
Adverse event, serious fatal	19
Consent withdrawn by subject	21
Adverse event, non-fatal	1
Other Reason	10
Study-specific withdrawal criteria	1
Lost to follow-up	8
Severe non-compliance	1

Baseline characteristics

Reporting groups	
Reporting group title	Benralizumab 10 mg
Reporting group description: Every 8 weeks administered subcutaneously	
Reporting group title	Benralizumab 30 mg
Reporting group description: Every 8 weeks administered subcutaneously	
Reporting group title	Benralizumab 100 mg
Reporting group description: Every 8 weeks administered subcutaneously	
Reporting group title	Placebo
Reporting group description: Every 8 weeks administered subcutaneously	

Reporting group values	Benralizumab 10 mg	Benralizumab 30 mg	Benralizumab 100 mg
Number of subjects	562	562	562
Age categorical Units: Subjects			
Adults (18-64 years)	263	241	275
From 65-84 years	298	319	286
85 years and over	1	2	1
Age Continuous Units: Years			
arithmetic mean	64.7	65.6	65.0
standard deviation	± 8.47	± 8.61	± 8.23
Sex: Female, Male Units: Subjects			
Female	196	194	207
Male	366	368	355
Race/Ethnicity, Customized Units: Subjects			
White|	441	444	443
Black or African American|	8	12	16
Asian|	70	69	67
Other|	43	37	36

Reporting group values	Placebo	Total	
Number of subjects	568	2254	
Age categorical Units: Subjects			
Adults (18-64 years)	261	1040	
From 65-84 years	307	1210	
85 years and over	0	4	
Age Continuous Units: Years			
arithmetic mean	65.3		

standard deviation	± 8.44	-	

Sex: Female, Male Units: Subjects			
Female	209	806	
Male	359	1448	
Race/Ethnicity, Customized Units: Subjects			
White|	446	1774	
Black or African American|	19	55	
Asian|	67	273	
Other|	36	152	

End points

End points reporting groups

Reporting group title	Benralizumab 10 mg
Reporting group description: Every 8 weeks administered subcutaneously	
Reporting group title	Benralizumab 30 mg
Reporting group description: Every 8 weeks administered subcutaneously	
Reporting group title	Benralizumab 100 mg
Reporting group description: Every 8 weeks administered subcutaneously	
Reporting group title	Placebo
Reporting group description: Every 8 weeks administered subcutaneously	

Primary: Annual COPD exacerbation rate ratio over 56 weeks treatment comparison for patients with baseline EOS>=220/uL

End point title	Annual COPD exacerbation rate ratio over 56 weeks treatment comparison for patients with baseline EOS>=220/uL
End point description: A COPD exacerbation is defined by symptomatic worsening of COPD requiring: • Use of systemic corticosteroids for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids; and/or • Use of antibiotics; and/or • An inpatient hospitalization or death due to COPD	
End point type	Primary
End point timeframe: Immediately following the first IP dose through week 56	

End point values	Benralizumab 10 mg	Benralizumab 30 mg	Benralizumab 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	377	394	386	388
Units: Rate of event over follow-up time				
least squares mean (confidence interval 95%)	0.99 (0.87 to 1.13)	1.21 (1.08 to 1.37)	1.09 (0.96 to 1.23)	1.17 (1.04 to 1.32)

Statistical analyses

Statistical analysis title	Negative binomial Analysis
Comparison groups	Benralizumab 10 mg v Placebo

Number of subjects included in analysis	765
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0638
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.01

Statistical analysis title	Negative binomial analysis
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	782
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6575
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.23

Statistical analysis title	Negative binomial analysis
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	774
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3988
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.1

Secondary: Annual COPD exacerbation rate ratio over 56 weeks treatment

comparison for patients with baseline EOS<220/uL	
End point title	Annual COPD exacerbation rate ratio over 56 weeks treatment comparison for patients with baseline EOS<220/uL

End point description:

A COPD exacerbation is defined by symptomatic worsening of COPD requiring: • Use of systemic corticosteroids for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids; and/or • Use of antibiotics; and/or • An inpatient hospitalization or death due to COPD

End point type	Secondary

End point timeframe:

Immediately following the first IP dose through week 56

End point values	Benralizumab 10 mg	Benralizumab 30 mg	Benralizumab 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	185	168	176	180
Units: Rate of event over follow-up time				
least squares mean (confidence interval 95%)	1.23 (1.03 to 1.46)	1.27 (1.05 to 1.53)	1.21 (1.00 to 1.45)	1.18 (0.98 to 1.41)

Statistical analyses

Statistical analysis title	Negative binomial analysis
Comparison groups	Benralizumab 10 mg v Placebo
Number of subjects included in analysis	365
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7564
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.32

Statistical analysis title	Negative binomial analysis
Comparison groups	Benralizumab 30 mg v Placebo

Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5573
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.37

Statistical analysis title	Negative binomial analysis
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8644
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.3

Secondary: Mean change from baseline to Week 56 in pre-bronchodilator FEV1 (L) value for patients with baseline EOS>=220/uL

End point title	Mean change from baseline to Week 56 in pre-bronchodilator FEV1 (L) value for patients with baseline EOS>=220/uL

End point description:

Pre-bronchodilator FEV1 (L) is collected at Weeks 0, 4, 8, 16, 24, 32, 40, 48, and 56. Baseline is the last non-missing value with quality (acceptable or borderline quality grade) prior to the first dose of study treatment.

End point type	Secondary

End point timeframe:

First IP up to end of treatment Week 56

End point values	Benralizumab 10 mg	Benralizumab 30 mg	Benralizumab 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	325	322	347	344
Units: Liter				
arithmetic mean (standard deviation)	0.021 (± 0.346)	0.011 (± 0.289)	0.033 (± 0.291)	0.016 (± 0.292)

Statistical analyses

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 10 mg v Placebo
Number of subjects included in analysis	669
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5043
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.029
upper limit	0.059

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7691
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.051
upper limit	0.037

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 100 mg v Placebo

Number of subjects included in analysis	691
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3767
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.024
upper limit	0.064

Secondary: Mean change from baseline in SGRQ total score for patients with baseline EOS>=220/uL

End point title	Mean change from baseline in SGRQ total score for patients with baseline EOS>=220/uL

End point description:

SGRQ is from 50-item PRO instrument. The SGRQ total score is expressed as a percentage of overall impairment, in which 100% means the worst possible health status and 0 indicates the best possible health status.

End point type	Secondary

End point timeframe:

First IP up to Week 56

End point values	Benralizumab 10 mg	Benralizumab 30 mg	Benralizumab 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	331	329	354	349
Units: Percentage				
arithmetic mean (standard deviation)	-7.733 (± 14.996)	-8.674 (± 17.910)	-7.257 (± 15.989)	-6.863 (± 16.344)

Statistical analyses

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 10 mg v Placebo
Number of subjects included in analysis	680
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3636
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.011

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.192
upper limit	1.171

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	678
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2106
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.388
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.562
upper limit	0.786

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	703
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5851
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.602
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.763
upper limit	1.56

Secondary: Mean change from baseline in CAT total score for patients with baseline EOS>=220/uL

End point title	Mean change from baseline in CAT total score for patients with baseline EOS>=220/uL

End point description:

CAT is an 8-item PRO developed to measure the impact of COPD on health status. The instrument uses semantic differential six-point response scales. A CAT total score is the sum of item responses. Score ranges from 0 to 40 with higher scores indicative of greater COPD impact on health status.

End point type	Secondary

End point timeframe:
First IP up to Week 56

End point values	Benralizumab 10 mg	Benralizumab 30 mg	Benralizumab 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	332	331	354	350
Units: Score on a scale				
arithmetic mean (standard deviation)	-2.18 (± 6.78)	-2.43 (± 7.18)	-2.36 (± 6.67)	-2.36 (± 6.54)

Statistical analyses

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 10 mg v Placebo
Number of subjects included in analysis	682
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8525
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	0.99

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	681
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.987
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	0.89

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	704
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8204
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.79

Secondary: Mean change from baseline in E-RS: COPD total score for patients with baseline EOS>=220/uL

End point title	Mean change from baseline in E-RS: COPD total score for patients with baseline EOS>=220/uL

End point description:

The E-RS: COPD is an 11-item PRO developed to evaluate the severity of respiratory symptoms of COPD. Summation of E-RS: COPD item responses produces a total score ranging from 0 to 40, with higher scores indicating greater severity.

End point type	Secondary

End point timeframe:

First IP up to Week 56

End point values	Benralizumab 10 mg	Benralizumab 30 mg	Benralizumab 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	316	302	317	325
Units: Score on a scale				
arithmetic mean (standard deviation)	-1.657 (± 5.701)	-2.219 (± 6.381)	-1.593 (± 5.665)	-1.137 (± 5.935)

Statistical analyses

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 10 mg v Placebo

Number of subjects included in analysis	641
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2636
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.102
upper limit	0.301

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	627
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4087
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.296
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.998
upper limit	0.406

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	642
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2336
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.425
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.125
upper limit	0.275

Secondary: Mean change from baseline in total rescue medication use (number of

puffs per day) for patients with baseline EOS>=220/uL	
End point title	Mean change from baseline in total rescue medication use (number of puffs per day) for patients with baseline EOS>=220/uL

End point description:

The number of rescue medication inhalations and nebulizer treatments taken are recorded by the patient in the eDiary twice daily. Total rescue medication use is the sum of daytime and night-time use.

End point type	Secondary

End point timeframe:

First IP up to Week 56

End point values	Benralizumab 10 mg	Benralizumab 30 mg	Benralizumab 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	305	290	310	314
Units: Puffs/day				
arithmetic mean (standard deviation)	-0.36 (± 3.04)	-0.24 (± 3.36)	-0.17 (± 3.02)	0.23 (± 3.55)

Statistical analyses

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 10 mg v Placebo
Number of subjects included in analysis	619
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0012
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.642
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.029
upper limit	-0.254

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0852
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.34

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.727
upper limit	0.047

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	624
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.065
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.364
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.75
upper limit	0.023

Secondary: Mean change from baseline in proportion of nights awakenings due to respiratory symptoms for patients with baseline EOS>=220/uL

End point title	Mean change from baseline in proportion of nights awakenings due to respiratory symptoms for patients with baseline EOS>=220/uL

End point description:

The number of rescue medication inhalations and nebulizer treatments taken are recorded by the patient in the eDiary twice daily. Total rescue medication use is the sum of daytime and night-time use.

End point type	Secondary

End point timeframe:

First IP up to Week 56

End point values	Benralizumab 10 mg	Benralizumab 30 mg	Benralizumab 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	316	298	321	322
Units: Proportion				
arithmetic mean (standard deviation)	-0.092 (± 0.297)	-0.131 (± 0.332)	-0.084 (± 0.334)	-0.053 (± 0.345)

Statistical analyses

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 10 mg v Placebo
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0415
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.041
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.081
upper limit	-0.002

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	643
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2008
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.065
upper limit	0.014

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	620
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0069
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.055
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.094
upper limit	-0.015

Secondary: Number of COPD exacerbations based on EXACT-PRO for patients with baseline EOS>=220/uL

End point title	Number of COPD exacerbations based on EXACT-PRO for patients with baseline EOS>=220/uL

End point description:

The EXACT-PRO is a 14-item PRO instrument developed to assess the frequency, severity and duration of COPD exacerbations. Respondents are instructed to complete the electronic diary (eDiary) each evening just prior to bedtime and to answer the questions while onsidering their experiences "today". The daily EXACT-PRO total score has a range of 0-100 with higher scores indicative of greater severity. Event frequency is calculated by comparing the baseline with daily total scores. An increase in EXACT-PRO total score ≥9 for 3 days or ≥12 for 2 days indicate an event has occurred.

End point type	Secondary

End point timeframe:

Immediately following first IP up to week 56

End point values	Benralizumab 10 mg	Benralizumab 30 mg	Benralizumab 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	377	394	385	388
Units: Participants				
0 exacerbation	166	173	162	159
1 exacerbation	108	107	113	119
2 exacerbations	45	51	56	46
3 exacerbations	21	27	25	27
4 exacerbations	14	16	13	13
5 exacerbations	8	8	9	12
6 exacerbations	7	6	4	7
7 exacerbations	2	4	1	2
8 exacerbations	4	1	2	1
9 exacerbations	0	1	0	1
10 exacerbations	2	0	0	0
11 exacerbations	0	0	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of EXACT-PRO for patients with baseline EOS>=220/uL

End point title	Severity of EXACT-PRO for patients with baseline EOS>=220/uL

End point description:

The EXACT-PRO is a 14-item PRO instrument developed to assess the frequency, severity and duration of COPD exacerbations. Respondents are instructed to complete the electronic diary (eDiary) each evening just prior to bedtime and to answer the questions while onsidering their experiences "today". The daily EXACT-PRO total score has a range of 0-100 with higher scores indicative of greater severity. Event frequency is calculated by comparing the baseline with daily total scores. An increase in EXACT-PRO total score ≥9 for 3 days or ≥12 for 2 days indicate an event has occurred. The severity of an event

is indicated by the worst (highest) EXACT-PRO total score during an event.

End point type	Secondary

End point timeframe:

Immediately following first IP up to week 56

End point values	Benralizumab 10 mg	Benralizumab 30 mg	Benralizumab 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	211	221	223	229
Units: Score on a scale				
arithmetic mean (standard deviation)	50.3 (± 12.30)	52.1 (± 11.3)	51.2 (± 11.0)	51.0 (± 11.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of EXACT-PRO for patients with baseline EOS>=220/uL

End point title	Duration of EXACT-PRO for patients with baseline EOS>=220/uL

End point description:

The EXACT-PRO is a 14-item PRO instrument developed to assess the frequency, severity and duration of COPD exacerbations. Respondents are instructed to complete the electronic diary (eDiary) each evening just prior to bedtime and to answer the questions while onsidering their experiences “today”. The daily EXACT-PRO total score has a range of 0-100 with higher scores indicative of greater severity. Event frequency is calculated by comparing the baseline with daily total scores. An increase in EXACT-PRO total score ≥9 for 3 days or ≥12 for 2 days indicate an event has occurred. Calculation of event duration after identification of the following five parameters: 1) onset; 2) three-day rolling average; 3) maximum observed value; 4) threshold for improvement; and 5) recovery.

End point type	Secondary

End point timeframe:

Immediately following first IP up to week 56

End point values	Benralizumab 10 mg	Benralizumab 30 mg	Benralizumab 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	211	221	223	229
Units: Days				
arithmetic mean (standard deviation)	110.1 (± 114.0)	96.1 (± 109.3)	99.8 (± 114.8)	99.9 (± 113.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Annual EXACT-PRO exacerbation rate ratio over 56 weeks treatment comparison for patients with baseline EOS>=220/uL

End point title	Annual EXACT-PRO exacerbation rate ratio over 56 weeks treatment comparison for patients with baseline EOS>=220/uL

End point description:

The EXACT-PRO is a 14-item PRO instrument developed to assess the frequency, severity and duration of COPD exacerbations. Respondents are instructed to complete the electronic diary (eDiary) each evening just prior to bedtime and to answer the questions while considering their experiences "today". The daily EXACT-PRO total score has a range of 0-100 with higher scores indicative of greater severity. Total score changes are used to identify the onset and recovery from an EXACT-PRO defined exacerbation event. An increase in EXACT-PRO total score ≥9 for 3 days or ≥12 for 2 days indicate an event has occurred.

End point type	Secondary

End point timeframe:

Immediately following the first IP dose through week 56

End point values	Benralizumab 10 mg	Benralizumab 30 mg	Benralizumab 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	377	394	385	388
Units: Rate of event over follow-up time				
least squares mean (confidence interval 95%)	1.20 (1.05 to 1.37)	1.21 (1.06 to 1.37)	1.13 (0.99 to 1.29)	1.23 (1.08 to 1.40)

Statistical analyses

Statistical analysis title	Negative binomial analysis
Comparison groups	Benralizumab 10 mg v Placebo
Number of subjects included in analysis	765
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8158
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.18

Statistical analysis title	Negative binomial analysis
Comparison groups	Benralizumab 30 mg v Placebo

Number of subjects included in analysis	782
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8378
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.18

Statistical analysis title	Negative bionomail analysis
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	773
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3759
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.11

Secondary: Number of participants having at least 1 COPD exacerbation for patients with baseline EOS>=220/uL

End point title	Number of participants having at least 1 COPD exacerbation for patients with baseline EOS>=220/uL

End point description:

A COPD exacerbation is defined by symptomatic worsening COPD requiring systemic corticosteroids, antibiotics, or an inpatient hospitalization/death due to COPD.

End point type	Secondary

End point timeframe:

Immediately following first IP dose up to week 56

End point values	Benralizumab 10 mg	Benralizumab 30 mg	Benralizumab 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	377	394	386	388
Units: Participants	203	241	214	208

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel Test (odds ratio)
Statistical analysis description: Proportion of participants with >=1 COPD exacerbation.	
Comparison groups	Benralizumab 10 mg v Placebo
Number of subjects included in analysis	765
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9141
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.36

Statistical analysis title	Cochran-Mantel-Haenszel Test (odds ratio)
Statistical analysis description: Proportion of participants with >=1 COPD exacerbation.	
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	782
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0323
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	1.87

Statistical analysis title	Cochran-Mantel-Haenszel Test (odds ratio)

Statistical analysis description:	
Proportion of participants with >=1 COPD exacerbation.	
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	774
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5109
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.48

Secondary: Time to first COPD exacerbation

End point title	Time to first COPD exacerbation
End point description:	
Time to first COPD exacerbation is from the randomization date to the first occurrence of COPD exacerbation.	
End point type	Secondary
End point timeframe:	
Immediately following first IP dose to week 56	

End point values	Benralizumab 10 mg	Benralizumab 30 mg	Benralizumab 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	377	394	386	388
Units: Days				
median (confidence interval 95%)	315 (244 to 380)	260 (225 to 291)	322 (278 to 373)	337 (261 to 400)

Statistical analyses

No statistical analyses for this end point

Secondary: Annual COPD exacerbation rate ratio associated with ER or hospitalization over 56 weeks treatment comparison for patients with baseline EOS>=220/uL

End point title	Annual COPD exacerbation rate ratio associated with ER or hospitalization over 56 weeks treatment comparison for patients with baseline EOS>=220/uL

End point description:

A COPD exacerbation is defined by symptomatic worsening COPD requiring systemic corticosteroids, antibiotics, or an inpatient hospitalization/death due to COPD.

End point type	Secondary

End point timeframe:

Immediately following the first IP dose through week 56

End point values	Benralizumab 10 mg	Benralizumab 30 mg	Benralizumab 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	377	394	386	388
Units: Rate of event over follow-up time				
least squares mean (confidence interval 95%)	0.22 (0.17 to 0.29)	0.29 (0.23 to 0.36)	0.22 (0.17 to 0.28)	0.32 (0.26 to 0.40)

Statistical analyses

Statistical analysis title	Negative binomial analysis
Comparison groups	Benralizumab 10 mg v Placebo
Number of subjects included in analysis	765
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0287
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.96

Statistical analysis title	Negative binomial analysis
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	782
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4631
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.22

Statistical analysis title	Negative binomial analysis
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	774
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0185
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	0.94

Secondary: Number of participants had COPD-related healthcare encounter for patient with baseline EOS>=220/uL

End point title	Number of participants had COPD-related healthcare encounter for patient with baseline EOS>=220/uL

End point description:

Types of healthcare encounter: Hospitalisations (inc. intensive care and/or general care), Emergency department visits, Unscheduled outpatients visits, Home visits, Telephone calls, and ambulance transports.

End point type	Secondary

End point timeframe:

Immediately following first IP dose up to Week 56

End point values	Benralizumab 10 mg	Benralizumab 30 mg	Benralizumab 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	377	394	386	388
Units: Participants				
Hospitalisations|	45	67	48	59
Emergency department|	49	72	58	71
Unscheduled outpatient visits|	208	230	225	211
Home visits|	14	20	17	14
Telephone calls|	98	112	109	114
Ambulance transports|	10	19	20	22

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of study treatment administration

End point title	Duration of study treatment administration

End point description:

Duration of study treatment is calculated from first dose date to last dose date + 1 day.

End point type	Secondary

End point timeframe:

From first dose date to last dose date

End point values	Benralizumab 10 mg	Benralizumab 30 mg	Benralizumab 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	561	562[1]	562	568
Units: Days				
arithmetic mean (standard deviation)	307.4 (± 80.38)	302.2 (± 84.62)	303.0 (± 88.48)	308.8 (± 78.95)

Notes:

[1] - 1 pat. rand. to 10 mg, but treated with 30 mg, so total 563 treated with 30 mg.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum concentration of Benralizumab

End point title	Serum concentration of Benralizumab[2]

End point description:

PK serum samples were collected pre-dose at each visit.

End point type	Secondary

End point timeframe:

From first dose to 1 cycle after discontinuation of treatment

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: It is not applicable for Placebo treatment group having Benralizumab concentration. Thus no data is available for this arm.

End point values	Benralizumab 10 mg	Benralizumab 30 mg	Benralizumab 100 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	558	560	552	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Baseline|	0 (± 0)	0 (± 0)	0 (± 51.95)	
Week 56|	42.51 (± 384.81)	222.92 (± 248.24)	594.33 (± 321.66)	

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity of Benralizumab

End point title	Immunogenicity of Benralizumab

End point description:

ADA responses such as ADA prevalence, ADA incidence, ADA persistently positive counts, etc. were presented.

End point type	Secondary

End point timeframe:

Pre-treatment until end of follow-up

End point values	Benralizumab 10 mg	Benralizumab 30 mg	Benralizumab 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	561	562[3]	562	568
Units: Participants				
ADA prevalence|	70	52	77	26
ADA incidence|	60	39	65	16
Both base/post-baseline positive|	9	8	5	10
Only post baseline|	57	38	64	14
Only baseline|	4	6	8	2
ADA persistently positive|	42	30	43	6
ADA transiently positive|	15	8	21	8
nAb prevalence|	55	37	59	13
nAb incidence|	50	33	52	9

Notes:

[3] - 1 pat. rand. to 10 mg, but treated with 30 mg, so total 563 treated with 30 mg.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug until last study visit	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Benra 10 mg
Reporting group description: -	
Reporting group title	Benra 30 mg
Reporting group description: -	
Reporting group title	Benra 100 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Benra 10 mg	Benra 30 mg	Benra 100 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	144 / 561 (25.67%)	177 / 563 (31.44%)	127 / 562 (22.60%)
number of deaths (all causes)	17	21	17
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Abdominal neoplasm			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myeloid leukaemia			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma gastric			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			

subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	1 / 561 (0.18%)	1 / 563 (0.18%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain cancer metastatic			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain neoplasm benign			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer female			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon adenoma			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal cancer metastatic			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Follicular thyroid cancer			

subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal squamous cell carcinoma			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip and/or oral cavity cancer			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung cancer metastatic			
subjects affected / exposed	1 / 561 (0.18%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 561 (0.00%)	2 / 563 (0.36%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic malignant melanoma			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine carcinoma metastatic			

subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Oesophageal adenocarcinoma stage 0			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	0 / 561 (0.00%)	2 / 563 (0.36%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pancreatic carcinoma metastatic			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polycythaemia vera			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	2 / 562 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal neoplasm			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			

subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the cervix			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sweat gland tumour			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid cancer			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell cancer of the renal pelvis and ureter			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic aneurysm			
subjects affected / exposed	1 / 561 (0.18%)	1 / 563 (0.18%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Aortic dissection			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			

subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory collapse			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	2 / 562 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			

subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Penetrating aortic ulcer			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 561 (0.18%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Oedema			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Food allergy			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Acquired hydrocele			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 561 (0.18%)	1 / 563 (0.18%)	2 / 562 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic prolapse			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatitis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			

subjects affected / exposed	3 / 561 (0.53%)	1 / 563 (0.18%)	4 / 562 (0.71%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Aspiration			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	92 / 561 (16.40%)	107 / 563 (19.01%)	80 / 562 (14.23%)
occurrences causally related to treatment / all	0 / 129	0 / 136	0 / 106
deaths causally related to treatment / all	0 / 1	0 / 4	0 / 5
Chronic respiratory failure			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	2 / 562 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystic lung disease			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	3 / 561 (0.53%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercapnia			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			

subjects affected / exposed	1 / 561 (0.18%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infiltration			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax spontaneous			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	6 / 561 (1.07%)	0 / 563 (0.00%)	3 / 562 (0.53%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary mass			

subjects affected / exposed	0 / 561 (0.00%)	2 / 563 (0.36%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	3 / 561 (0.53%)	2 / 563 (0.36%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcoholism			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bipolar disorder			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			

subjects affected / exposed	2 / 561 (0.36%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post-traumatic stress disorder			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Anticoagulation drug level above therapeutic			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
False positive tuberculosis test			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio			

increased			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oxygen saturation decreased			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Abdominal injury			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia postoperative			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carbon monoxide poisoning			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Femur fracture			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Open fracture			

subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic fracture			
subjects affected / exposed	1 / 561 (0.18%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haemorrhage			

subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 561 (0.18%)	1 / 563 (0.18%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	2 / 561 (0.36%)	7 / 563 (1.24%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 2	2 / 7	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Angina pectoris			
subjects affected / exposed	2 / 561 (0.36%)	1 / 563 (0.18%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	3 / 561 (0.53%)	2 / 563 (0.36%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	1 / 3	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve incompetence			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	2 / 561 (0.36%)	1 / 563 (0.18%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 561 (0.18%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			

subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 561 (0.00%)	2 / 563 (0.36%)	3 / 562 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac failure acute			
subjects affected / exposed	2 / 561 (0.36%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Cardiac failure chronic			
subjects affected / exposed	1 / 561 (0.18%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	3 / 561 (0.53%)	2 / 563 (0.36%)	4 / 562 (0.71%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	1 / 561 (0.18%)	1 / 563 (0.18%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Cor pulmonale			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 561 (0.18%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	3 / 561 (0.53%)	1 / 563 (0.18%)	3 / 562 (0.53%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Right ventricular failure			
subjects affected / exposed	0 / 561 (0.00%)	2 / 563 (0.36%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular extrasystoles			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Carotid arteriosclerosis			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar haemorrhage			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cerebrovascular accident			

subjects affected / exposed	1 / 561 (0.18%)	4 / 563 (0.71%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cervical myelopathy			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disorder			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia Alzheimer's type			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	2 / 562 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	2 / 562 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Hepatic encephalopathy			

subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intercostal neuralgia			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial aneurysm			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 561 (0.18%)	1 / 563 (0.18%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbosacral radiculopathy			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis relapse			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myoclonus			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	2 / 561 (0.36%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombotic cerebral infarction			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	2 / 561 (0.36%)	1 / 563 (0.18%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 561 (0.00%)	2 / 563 (0.36%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic anaemia			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polycythaemia			

subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal artery embolism			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal incarcerated hernia			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	2 / 561 (0.36%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic gastritis			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 561 (0.00%)	2 / 563 (0.36%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Colonic pseudo-obstruction			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenitis			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral hernia strangulated			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			

subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal polyp haemorrhage			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 561 (0.00%)	2 / 563 (0.36%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			

subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar hernia			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal hypomotility			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 561 (0.00%)	2 / 563 (0.36%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eczema			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Henoch-Schonlein purpura			

subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriasis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 561 (0.71%)	0 / 563 (0.00%)	2 / 562 (0.36%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal infarct			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			

subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriatic arthropathy			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trigger finger			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Abdominal abscess			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute sinusitis			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 561 (0.18%)	2 / 563 (0.36%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 561 (0.00%)	4 / 563 (0.71%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis bacterial			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis infective			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site cellulitis			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 561 (0.36%)	2 / 563 (0.36%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			

subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea infectious			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 561 (0.18%)	1 / 563 (0.18%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis C			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	2 / 562 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious colitis			

subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 561 (0.18%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal sepsis			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Labyrinthitis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lung infection			

subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	2 / 562 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	19 / 561 (3.39%)	22 / 563 (3.91%)	9 / 562 (1.60%)
occurrences causally related to treatment / all	0 / 20	0 / 25	1 / 10
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 0
Pneumonia bacterial			
subjects affected / exposed	5 / 561 (0.89%)	5 / 563 (0.89%)	2 / 562 (0.36%)
occurrences causally related to treatment / all	0 / 5	0 / 7	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomembranous colitis			

subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonas bronchitis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 561 (0.00%)	2 / 563 (0.36%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary tuberculosis			
subjects affected / exposed	1 / 561 (0.18%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	3 / 561 (0.53%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheobronchitis			
subjects affected / exposed	1 / 561 (0.18%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tuberculosis			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			

subjects affected / exposed	1 / 561 (0.18%)	1 / 563 (0.18%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 561 (0.18%)	2 / 563 (0.36%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Alcohol intolerance			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cachexia			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			

subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 561 (0.18%)	0 / 563 (0.00%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 561 (0.00%)	0 / 563 (0.00%)	1 / 562 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	0 / 561 (0.00%)	1 / 563 (0.18%)	0 / 562 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	158 / 568 (27.82%)		
number of deaths (all causes)	19		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Abdominal neoplasm			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute myeloid leukaemia			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma gastric			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Adenocarcinoma of colon			
subjects affected / exposed	1 / 568 (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 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder cancer			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain cancer metastatic			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Brain neoplasm benign			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast cancer female			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colon adenoma			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colorectal cancer metastatic			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Follicular thyroid cancer			

subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laryngeal squamous cell carcinoma				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lip and/or oral cavity cancer				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung adenocarcinoma				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung cancer metastatic				
subjects affected / exposed	2 / 568 (0.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Lung neoplasm malignant				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastases to central nervous system				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastatic malignant melanoma				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neuroendocrine carcinoma metastatic				

subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal adenocarcinoma stage 0				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma metastatic				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Polycythaemia vera				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal cell carcinoma				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal neoplasm				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of lung				

subjects affected / exposed	1 / 568 (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	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sweat gland tumour				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thyroid cancer				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transitional cell cancer of the renal pelvis and ureter				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Accelerated hypertension				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aortic aneurysm				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aortic dissection				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aortic stenosis				

subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arteriosclerosis			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Circulatory collapse			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematoma			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	2 / 568 (0.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypovolaemic shock			

subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Orthostatic hypotension				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Penetrating aortic ulcer				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Multiple organ dysfunction syndrome				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema				
subjects affected / exposed	1 / 568 (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 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Food allergy			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Acquired hydrocele			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic prolapse			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prostatitis			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			

subjects affected / exposed	5 / 568 (0.88%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 2			
Aspiration				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atelectasis				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	89 / 568 (15.67%)			
occurrences causally related to treatment / all	0 / 140			
deaths causally related to treatment / all	0 / 2			
Chronic respiratory failure				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cystic lung disease				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypercapnia				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoxia				

subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung disorder				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infiltration				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	2 / 568 (0.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	2 / 568 (0.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumothorax spontaneous				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary mass				

subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Psychiatric disorders				
Alcohol abuse				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Alcoholism				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anxiety				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bipolar disorder				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Delirium				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Depression				

subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Major depression				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post-traumatic stress disorder				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Anticoagulation drug level above therapeutic				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Electrocardiogram T wave inversion				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
False positive tuberculosis test				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic enzyme increased				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
International normalised ratio				

increased				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oxygen saturation decreased				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Abdominal injury				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anaemia postoperative				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ankle fracture				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Carbon monoxide poisoning				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Concussion				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Femur fracture			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Foot fracture			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Forearm fracture			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hand fracture			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Laceration			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lumbar vertebral fracture			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Open fracture			

subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Procedural pain				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Toxicity to various agents				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Traumatic fracture				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Traumatic haemorrhage				

subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	3 / 568 (0.53%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Acute myocardial infarction			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Angina pectoris			
subjects affected / exposed	2 / 568 (0.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aortic valve incompetence			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block			

subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	2 / 568 (0.35%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cardiac failure acute				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure chronic				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	4 / 568 (0.70%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cor pulmonale				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				

subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Right ventricular failure				
subjects affected / exposed	2 / 568 (0.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sinus tachycardia				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ventricular extrasystoles				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular fibrillation				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Carotid arteriosclerosis				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebellar haemorrhage				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				

subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cervical myelopathy				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cognitive disorder				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dementia Alzheimer's type				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic stroke				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic encephalopathy				

subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intercostal neuralgia			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intracranial aneurysm			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	2 / 568 (0.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Lumbosacral radiculopathy			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple sclerosis relapse			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myoclonus			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			

subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombotic cerebral infarction				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vertebrobasilar insufficiency				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Disseminated intravascular coagulation				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic anaemia				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Iron deficiency anaemia				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Polycythaemia				

subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal artery embolism			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal incarcerated hernia			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	2 / 568 (0.35%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Chronic gastritis			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis ulcerative			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Colonic pseudo-obstruction			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticular perforation			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulum			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulum intestinal			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenitis			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femoral hernia strangulated			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			

subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal polyp haemorrhage				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematochezia				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Incarcerated inguinal hernia				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				

subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal perforation				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lumbar hernia				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal hypomotility				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				

subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis chronic			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eczema			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Henoch-Schonlein purpura			

subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psoriasis				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	3 / 568 (0.53%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 2			
Chronic kidney disease				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Renal infarct				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ureterolithiasis				

subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lumbar spinal stenosis			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psoriatic arthropathy			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spondylolisthesis			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Trigger finger			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Abdominal abscess			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute sinusitis			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	3 / 568 (0.53%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Bronchitis bacterial			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bursitis infective			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Catheter site cellulitis			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile colitis			

subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea infectious				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis C				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infectious colitis				

subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal sepsis			
subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Labyrinthitis			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Laryngitis			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Localised infection			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung abscess			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung infection			

subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	30 / 568 (5.28%)			
occurrences causally related to treatment / all	0 / 34			
deaths causally related to treatment / all	0 / 3			
Pneumonia bacterial				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia mycoplasmal				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural infection				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pseudomembranous colitis				

subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pseudomonas bronchitis				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary sepsis				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary tuberculosis				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tracheobronchitis				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tuberculosis				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				

subjects affected / exposed	4 / 568 (0.70%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 568 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral upper respiratory tract infection				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Alcohol intolerance				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cachexia				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus				
subjects affected / exposed	0 / 568 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	2 / 568 (0.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				

subjects affected / exposed	1 / 568 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	0 / 568 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Benra 10 mg	Benra 30 mg	Benra 100 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	365 / 561 (65.06%)	382 / 563 (67.85%)	368 / 562 (65.48%)
Vascular disorders			
Hypertension			
subjects affected / exposed	17 / 561 (3.03%)	16 / 563 (2.84%)	12 / 562 (2.14%)
occurrences (all)	22	17	12
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 561 (3.39%)	16 / 563 (2.84%)	27 / 562 (4.80%)
occurrences (all)	20	17	34
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	15 / 561 (2.67%)	9 / 563 (1.60%)	17 / 562 (3.02%)
occurrences (all)	17	9	18
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	8 / 561 (1.43%)	10 / 563 (1.78%)	20 / 562 (3.56%)
occurrences (all)	10	13	24
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	11 / 561 (1.96%)	12 / 563 (2.13%)	17 / 562 (3.02%)
occurrences (all)	11	12	20
Infections and infestations			
Bronchitis			
subjects affected / exposed	66 / 561 (11.76%)	70 / 563 (12.43%)	63 / 562 (11.21%)
occurrences (all)	94	100	87
Influenza			
subjects affected / exposed	11 / 561 (1.96%)	20 / 563 (3.55%)	15 / 562 (2.67%)
occurrences (all)	11	22	15
Lower respiratory tract infection			
subjects affected / exposed	26 / 561 (4.63%)	22 / 563 (3.91%)	15 / 562 (2.67%)
occurrences (all)	27	29	16
Oral candidiasis			
subjects affected / exposed	21 / 561 (3.74%)	12 / 563 (2.13%)	15 / 562 (2.67%)
occurrences (all)	25	13	20
Sinusitis			
subjects affected / exposed	15 / 561 (2.67%)	13 / 563 (2.31%)	15 / 562 (2.67%)
occurrences (all)	18	19	21
Upper respiratory tract infection			
subjects affected / exposed	68 / 561 (12.12%)	71 / 563 (12.61%)	67 / 562 (11.92%)
occurrences (all)	109	98	92
Urinary tract infection			
subjects affected / exposed	24 / 561 (4.28%)	24 / 563 (4.26%)	28 / 562 (4.98%)
occurrences (all)	34	26	32
Viral upper respiratory tract infection			
subjects affected / exposed	61 / 561 (10.87%)	47 / 563 (8.35%)	60 / 562 (10.68%)
occurrences (all)	73	68	92

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	378 / 568 (66.55%)		

Vascular disorders Hypertension subjects affected / exposed occurrences (all)	 21 / 568 (3.70%) 22		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 24 / 568 (4.23%) 36		
General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all)	 9 / 568 (1.58%) 10		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	 24 / 568 (4.23%) 34		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 15 / 568 (2.64%) 15		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Lower respiratory tract infection subjects affected / exposed occurrences (all) Oral candidiasis subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all)	 66 / 568 (11.62%) 88 11 / 568 (1.94%) 12 21 / 568 (3.70%) 27 12 / 568 (2.11%) 17 20 / 568 (3.52%) 24		

Upper respiratory tract infection subjects affected / exposed occurrences (all)	65 / 568 (11.44%) 89		
Urinary tract infection subjects affected / exposed occurrences (all)	18 / 568 (3.17%) 22		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	70 / 568 (12.32%) 93		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 April 2014	o Changed population from 'severe to very severe' to 'Moderate to very severe' o Inclusion criteria amended from FEV1 <50% to >20% and ≤65%; and exac history from >/=1 to >/= 2 moderate or >/=1 severe o Added sites, extended projected LSLV from Q2-17 to Q4-17 o Revised secondary endpoint from 'COPD specific resource utilization' to annual rate of hosp visits, ED visits, unscheduled study visits, other unscheduled visits due to COPD o Exclusion criteria for prior SCS/antibiotics/hosp changed from 8 weeks prior to enrolment to 2 weeks prior o Added excl criterion for ALT/AST >1.5x ULN (was previously just for hepatic disease) o Removed local eos measurement at V3 used for randomization stratification o Added adjudication of MACE
10 February 2015	o Added sites; reduced N to 1566/2088 {was originally 1743/2324} o Added exploratory CGIC and PGIC o Clarified Excl #23, to exclude history of immunodeficiency disorder and/or hep B/C as exclusion and allow patients with history of hep B vaccination without history of hepatitis o Section 3.5 entirely revised to clarify on con meds and restrictions, added requirement to captured COPD background meds for past year o Shift ePRO dispensing from V1 to V2 o Added collection of historical eos (from past year) if available o Amended to specify sequence of enrolment procedures when the low eos stratum is closed at site or country level (to allow ample time between V1-2 to receive central lab result, SF low eos pts) o Added clarity for re-screening (once per subject, discuss other reasons with STP) o Specified minimal time between doses (3wks) and procedures if need to postpone IP dosing o Added adjudication of malignancies
03 July 2015	o ≥220/µL now considered the boundary for the primary and the two key secondary efficacy variables analysis o Three baseline eosinophil count cohorts: ≥300/µL; 220-299/µL; <220/µL o Approximately 2:1 ratio of subjects above and below the boundary of 220/µL (rather than 300) o Defined sample size for each cohort, increased overall N to 1626/2168 for Galathea/Terranova; added sites o TB exclusion refined to specify first positive test must be treated according to guidelines before being considered for enrolment o One additional re-screening allowed for eos stratum closure, to be discussed with STP (NB: 'reason for change' indicates for pts with borderline eos, but CSP text doesn't stipulate that) o Specify that nAb will be tested on all ADA positive samples (instead of at EOT/FU/IPD timepoints) o All subgroup analyses will be described in the SAP

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported