Clinical trial results:
Randomised, double-blind, 56 week placebo-controlled, parallel group, multicentre, phase 3 study to evaluate the efficacy and safety of 2 doses of benralizumab in patients with moderate to very severe COPD with a history of exacerbations

Summary

EudraCT number	2013-004590-27
Trial protocol	CZ DE HU GB IT NL PL AT ES
Global end of trial date	10 April 2018

Results information

Result version number	v1 (current)
This version publication date	04 April 2019
First version publication date	04 April 2019

Trial information

Trial identification

Sponsor protocol code	D3251C00003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02138916
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	10 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 April 2018
Global end of trial reached?	Yes
Global end of trial date	10 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 subjects with moderate to severe COPD

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	13 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	Austria: 39
Country: Number of subjects enrolled	Canada: 65
Country: Number of subjects enrolled	Czech Republic: 37
Country: Number of subjects enrolled	Germany: 129
Country: Number of subjects enrolled	Hungary: 116
Country: Number of subjects enrolled	Italy: 34
Country: Number of subjects enrolled	Netherlands: 27
Country: Number of subjects enrolled	Poland: 176
Country: Number of subjects enrolled	Romania: 67
Country: Number of subjects enrolled	Russian Federation: 233
Country: Number of subjects enrolled	South Africa: 29
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 46
Country: Number of subjects enrolled	Spain: 54
Country: Number of subjects enrolled	Switzerland: 36
Country: Number of subjects enrolled	United Kingdom: 75
Country: Number of subjects enrolled	United States: 402
Country: Number of subjects enrolled	Japan: 91

Worldwide total number of subjects	1656
EEA total number of subjects	754

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)	716
From 65 to 84 years	939
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

4462 patients signed informed consent. 1656 patients randomized to Benralizumab 30 mg, Benralizumab 100 mg, or Placebo. All randomized patients were treated. 554 (33.5%) were randomized to Benralizumab 30 mg, 552 (33.3%) were randomized to Benralizumab 100 mg, and 550 (33.2%) were randomized to Placebo.

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 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 injection 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 30 mg	Benralizumab 100 mg	Placebo
Started	554	552	550
Completed	497	492	491
Not completed	57	60	59
Adverse event, serious fatal	14	11	12
Consent withdrawn by subject	27	31	32
incorrect enrolment	1	1	-
Adverse event, non-fatal	4	4	3
eg., meds change, lack of efficacy, etc.	6	9	7
Lost to follow-up	4	2	3
Study specific withdrawal criteria	-	-	1
Severe non-compliance	1	2	1

Baseline characteristics

Reporting groups	
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 30 mg	Benralizumab 100 mg	Placebo
Number of subjects	554	552	550
Age categorical Units: Subjects			
Adults (18-64 years)	231	231	254
From 65-84 years	323	320	296
85 years and over	0	1	0
Age Continuous Units: Year			
arithmetic mean	65.9	65.3	65.2
standard deviation	± 7.77	± 8.05	± 8.22
Sex: Female, Male Units: Subjects			
Female	172	180	175
Male	382	372	375
Race/Ethnicity, Customized Units: Subjects			
White	496	493	488
Black or African American	4	11	10
Asian	48	46	46
Other	6	2	6

Reporting group values	Total		
Number of subjects	1656		
Age categorical Units: Subjects			
Adults (18-64 years)	716		
From 65-84 years	939		
85 years and over	1		
Age Continuous Units: Year			
arithmetic mean			
standard deviation	-		

Sex: Female, Male Units: Subjects			
Female	527		
Male	1129		
Race/Ethnicity, Customized Units: Subjects			
White	1477		
Black or African American	25		
Asian	140		
Other	14		

End points

End points reporting groups

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:	
From first IP to week 56	

End point values	Benralizumab 30 mg	Benralizumab 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	382	379	359	
Units: Rate of event over follow-up time				
least squares mean (confidence interval 95%)	1.19 (1.04 to 1.36)	1.03 (0.9 to 1.19)	1.24 (1.08 to 1.42)	

Statistical analyses

Statistical analysis title	Negative binomial Analysis
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	741
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.649
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.96

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.15

Statistical analysis title	Negative binomial Analysis
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	738
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0525
Method	Negative binomial
Parameter estimate	Risk ratio (RR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	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:

From first IP to week 56

End point values	Benralizumab 30 mg	Benralizumab 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	173	191	
Units: Rate of event over follow-up time				
least squares mean (confidence interval 95%)	1.4 (1.19 to 1.64)	1.32 (1.12 to 1.56)	1.30 (1.11 to 1.52)	

Statistical analyses

Statistical analysis title	Negative binomial Analysis
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5236
Method	Negative binomial
Parameter estimate	Risk ratio (RR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.34

Statistical analysis title	Negative binomial Analysis
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	364
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8812
Method	Negative binomial
Parameter estimate	Risk ratio (RR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.27

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 30 mg	Benralizumab 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	329	326	317	
Units: Liter				
arithmetic mean (standard deviation)	0.014 (± 0.282)	0.031 (± 0.294)	0.010 (± 0.275)	

Statistical analyses

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	646
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.755
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.035
upper limit	0.048

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	= 0.3285
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.021
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.021
upper limit	0.062

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 30 mg	Benralizumab 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	338	331	317	
Units: Percentage				
arithmetic mean (standard deviation)	-5.025 (± 14.677)	-6.723 (± 15.723)	-3.913 (± 15.039)	

Statistical analyses

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	655
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2906
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.887
upper limit	0.865

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	648
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0264
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.136

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.02
upper limit	-0.251

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 30 mg	Benralizumab 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	338	335	319	
Units: Score on a scale				
arithmetic mean (standard deviation)	-1.50 (± 6.89)	-2.43 (± 6.34)	-1.22 (± 6.53)	

Statistical analyses

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	657
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6782
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.08
upper limit	0.7

Statistical analysis title	Mix effect repeated measurement analysis

Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	654
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0753
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	0.08

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 30 mg	Benralizumab 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	324	328	295	
Units: Score on a scale				
arithmetic mean (standard deviation)	-1.085 (± 5.273)	-1.354 (± 5.599)	-0.504 (± 5.674)	

Statistical analyses

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	619
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0889
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.585

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.26
upper limit	0.089

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	623
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0413
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.703
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.378
upper limit	-0.028

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 30 mg	Benralizumab 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	321	322	291	
Units: Puffs/day				
arithmetic mean (standard deviation)	-0.05 (± 3.21)	-0.27 (± 2.71)	0.29 (± 3.03)	

Statistical analyses

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	612
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0728
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.348
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.728
upper limit	0.032

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	613
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0121
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.487
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.868
upper limit	-0.107

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 30 mg	Benralizumab 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	325	323	297	
Units: Proportion				
arithmetic mean (standard deviation)	-0.088 (± 0.310)	-0085 (± 0.283)	-0.049 (± 0.307)	

Statistical analyses

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	622
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0235
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.041
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.077
upper limit	-0.006

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	620
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0158
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.044
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	-0.008

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 30 mg	Benralizumab 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	382	378	358	
Units: Participants				
0 exacerbation	180	184	179	
1 exacerbation	101	103	99	
2 exacerbations	42	49	34	
3 exacerbations	25	14	15	
4 exacerbations	17	13	14	
5 exacerbations	5	6	5	
6 exacerbations	4	4	2	
7 exacerbations	6	1	5	
8 exacerbations	1	1	4	
9 exacerbations	1	2	1	
10 exacerbations	0	1	0	

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 30 mg	Benralizumab 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	202	194	179	
Units: Score on a scale				
arithmetic mean (standard deviation)	51.5 (± 11.30)	50.8 (± 10.70)	52.0 (± 11.20)	

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 30 mg	Benralizumab 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	202	194	179	
Units: Days				
arithmetic mean (standard deviation)	82.2 (± 95.80)	88.3 (± 105.30)	101.7 (± 113.70)	

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 first IP up to week 56

End point values	Benralizumab 30 mg	Benralizumab 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	382	378	358	
Units: Rate of event over follow-up time				
least squares mean (confidence interval 95%)	1.14 (0.98 to 1.31)	1.02 (0.88 to 1.19)	1.04 (0.90 to 1.21)	

Statistical analyses

Statistical analysis title	Negative binomial analysis
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	740
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.408
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.34

Statistical analysis title	Negative binomial analysis
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	736
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8688
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.21

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 up to week 56

End point values	Benralizumab 30 mg	Benralizumab 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	382	379	359	
Units: Participants	204	203	198	

Statistical analyses

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	741
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.485
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.22

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	738
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4489
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.21

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 up to week 56

End point values	Benralizumab 30 mg	Benralizumab 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	382	379	359	
Units: Days				
median (confidence interval 95%)	333 (273 to 400)	329 (262 to 396)	337 (261 to 390)	

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 first IP up to week 56

End point values	Benralizumab 30 mg	Benralizumab 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	382	379	359	
Units: Rate of event over follow-up time				
least squares mean (confidence interval 95%)	0.27 (0.20 to 0.35)	0.15 (0.11 to 0.20)	0.25 (0.19 to 0.33)	

Statistical analyses

Statistical analysis title	Negative binomial analysis
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	741
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7733
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.53

Statistical analysis title	Negative binomial analysis
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	738
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0114
Method	Nagative binomial
Parameter estimate	Rate ratio
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.89

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 up to week 56

End point values	Benralizumab 30 mg	Benralizumab 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	382	379	359	
Units: Participants				
Hospitalisations|	60	38	50	
Emergency Department Visits|	36	35	43	
Unscheduled Outpatient Visits|	219	236	202	
Home Visits|	18	22	18	
Telephone calls|	110	111	104	
Ambulance transports|	16	12	20	

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 30 mg	Benralizumab 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	554	552	550	
Units: Days				
arithmetic mean (standard deviation)	302.4 (± 85.73)	304.0 (± 82.40)	302.5 (± 88.47)	

Statistical analyses

No statistical analyses for this end point

Secondary: Serum concentration of Benralizumab

End point title	Serum concentration of Benralizumab[1]

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:

[1] - 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: This summary is on the serum concentration of Benralizumab, thus the placebo group is not applicable.

End point values	Benralizumab 30 mg	Benralizumab 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	553	550		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Baseline|	0 (± 0)	0 (± 0)		
Week 56|	219.45 (± 233.21)	699.89 (± 243.20)		

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 30 mg	Benralizumab 100 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	554	552	550	
Units: Participants				
ADA prevalence|	53	64	39	
ADA incidence|	44	47	24	
Both base/post-baseline positive|	5	7	17	
Only post baseline positive|	43	46	20	
Only baseline positive|	5	11	2	
ADA persistently positive|	28	34	14	
ADA transiently positive|	15	12	6	
nAb prevalence|	43	43	25	
nAb incidence|	41	37	18	

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	Benralizumab 30 mg
Reporting group description: -	
Reporting group title	Benralizumab 100 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Benralizumab 30 mg	Benralizumab 100 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	151 / 554 (27.26%)	177 / 552 (32.07%)	176 / 550 (32.00%)
number of deaths (all causes)	15	12	13
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Adenocarcinoma of colon			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	2 / 550 (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
Basal cell carcinoma			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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 lung neoplasm			

subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Bladder cancer			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Colon neoplasm			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Glioblastoma multiforme			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Haemangioma of skin			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Laryngeal squamous cell carcinoma			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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 / 554 (0.00%)	1 / 552 (0.18%)	2 / 550 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			

subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Meningioma			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Non-small cell lung cancer			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Non-small cell lung cancer metastatic			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Non-small cell lung cancer stage IIIB			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Pancreatic carcinoma			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Plasma cell myeloma			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Prostate cancer			
subjects affected / exposed	2 / 554 (0.36%)	1 / 552 (0.18%)	2 / 550 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer stage II			

subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Renal neoplasm			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Sarcoma			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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 cell lung cancer			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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 cell lung cancer metastatic			
subjects affected / exposed	0 / 554 (0.00%)	2 / 552 (0.36%)	0 / 550 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	1 / 550 (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
Tonsil cancer			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Transitional cell carcinoma			
subjects affected / exposed	2 / 554 (0.36%)	0 / 552 (0.00%)	0 / 550 (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
Vascular disorders			
Arterial haemorrhage			

subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	3 / 550 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	1 / 550 (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
Hypertensive crisis			
subjects affected / exposed	1 / 554 (0.18%)	1 / 552 (0.18%)	0 / 550 (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
Hypotension			
subjects affected / exposed	0 / 554 (0.00%)	2 / 552 (0.36%)	0 / 550 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	2 / 550 (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
Peripheral ischaemia			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Peripheral venous disease			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
General disorders and administration site conditions			
Chest discomfort			

subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Death			
subjects affected / exposed	1 / 554 (0.18%)	1 / 552 (0.18%)	1 / 550 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Non-cardiac chest pain			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Oedema peripheral			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Sudden cardiac death			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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			

Benign prostatic hyperplasia			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	1 / 550 (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
Endometriosis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Prostatitis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	2 / 550 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bronchiectasis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Bronchitis chronic			
subjects affected / exposed	1 / 554 (0.18%)	1 / 552 (0.18%)	1 / 550 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	97 / 554 (17.51%)	78 / 552 (14.13%)	100 / 550 (18.18%)
occurrences causally related to treatment / all	5 / 145	1 / 101	0 / 142
deaths causally related to treatment / all	0 / 7	0 / 1	0 / 2
Chronic respiratory failure			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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	1 / 554 (0.18%)	0 / 552 (0.00%)	1 / 550 (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 / 1
Hypercapnia			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	1 / 550 (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
Hypoxia			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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 consolidation			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Pickwickian syndrome			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Pneumonia aspiration			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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			
subjects affected / exposed	2 / 554 (0.36%)	1 / 552 (0.18%)	5 / 550 (0.91%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 6
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumothorax spontaneous			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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	1 / 554 (0.18%)	1 / 552 (0.18%)	4 / 550 (0.73%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 5
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 2
Pulmonary fibrosis			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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 hypertension			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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 mass			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Respiratory failure			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	3 / 550 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety disorder			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Depression			

subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Mental status changes			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Investigations			
Electrocardiogram ST-T change			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Injury, poisoning and procedural complications			
Airway burns			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Ankle fracture			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Arterial bypass occlusion			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Asbestosis			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Chest injury			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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

Dural tear			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Facial bones fracture			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Femur fracture			
subjects affected / exposed	0 / 554 (0.00%)	2 / 552 (0.36%)	0 / 550 (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
Foot fracture			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Fractured coccyx			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Hip fracture			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Joint dislocation			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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 limb fracture			

subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Patella fracture			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Rib fracture			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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 flap necrosis			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Spinal compression fracture			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	1 / 550 (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
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Subdural haematoma			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Tendon rupture			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Thoracic vertebral fracture			

subjects affected / exposed	1 / 554 (0.18%)	1 / 552 (0.18%)	1 / 550 (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
Traumatic haematoma			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Upper limb fracture			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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 bypass dysfunction			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Vascular graft occlusion			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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 procedure complication			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Wound			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Wound dehiscence			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Congenital, familial and genetic disorders			
Exomphalos			

subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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 myocardial infarction			
subjects affected / exposed	2 / 554 (0.36%)	1 / 552 (0.18%)	4 / 550 (0.73%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute right ventricular failure			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Angina pectoris			
subjects affected / exposed	1 / 554 (0.18%)	3 / 552 (0.54%)	0 / 550 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	2 / 554 (0.36%)	2 / 552 (0.36%)	2 / 550 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve disease			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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 valve stenosis			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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	4 / 554 (0.72%)	8 / 552 (1.45%)	2 / 550 (0.36%)
occurrences causally related to treatment / all	0 / 4	0 / 8	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	2 / 550 (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
Atrioventricular block complete			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	1 / 550 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	1 / 550 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	3 / 554 (0.54%)	2 / 552 (0.36%)	1 / 550 (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
Cardiac failure acute			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	1 / 550 (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 / 0
Cardiac failure congestive			
subjects affected / exposed	2 / 554 (0.36%)	2 / 552 (0.36%)	1 / 550 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Cor pulmonale chronic			

subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Coronary artery disease			
subjects affected / exposed	1 / 554 (0.18%)	1 / 552 (0.18%)	0 / 550 (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
Coronary artery insufficiency			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Coronary artery occlusion			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Coronary artery stenosis			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	3 / 550 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Myocardial infarction			
subjects affected / exposed	4 / 554 (0.72%)	3 / 552 (0.54%)	1 / 550 (0.18%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Myocarditis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Supraventricular tachycardia			

subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	2 / 550 (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
Cerebral infarction			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Cerebral ischaemia			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Cerebrovascular accident			
subjects affected / exposed	2 / 554 (0.36%)	1 / 552 (0.18%)	0 / 550 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	1 / 550 (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
Facial paralysis			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Hyperaesthesia			

subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	1 / 550 (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
Ischaemic stroke			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Lumbar radiculopathy			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Metabolic encephalopathy			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Monoparesis			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Neuropathy peripheral			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Polyneuropathy			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Radicular syndrome			

subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Radiculopathy			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Sciatica			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Seizure			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Sinus headache			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Stupor			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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	1 / 554 (0.18%)	1 / 552 (0.18%)	0 / 550 (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
Thrombotic stroke			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Transient ischaemic attack			

subjects affected / exposed	0 / 554 (0.00%)	2 / 552 (0.36%)	0 / 550 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	2 / 550 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypochromic anaemia			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Iron deficiency anaemia			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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 wall haematoma			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Ascites			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Colitis			
subjects affected / exposed	0 / 554 (0.00%)	2 / 552 (0.36%)	1 / 550 (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 / 0
Constipation			
subjects affected / exposed	2 / 554 (0.36%)	1 / 552 (0.18%)	0 / 550 (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
Diverticulum			

subjects affected / exposed	0 / 554 (0.00%)	2 / 552 (0.36%)	0 / 550 (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
Enterocolitis			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Gastric polyps			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Gastritis			
subjects affected / exposed	1 / 554 (0.18%)	1 / 552 (0.18%)	0 / 550 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	2 / 550 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal necrosis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Haematochezia			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Haemorrhoids			

subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Ileus			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Inguinal hernia			
subjects affected / exposed	0 / 554 (0.00%)	3 / 552 (0.54%)	0 / 550 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Intestinal perforation			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Intestinal polyp			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Irritable bowel syndrome			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Large intestine perforation			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Large intestine polyp			

subjects affected / exposed	0 / 554 (0.00%)	2 / 552 (0.36%)	2 / 550 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Melaena			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Nausea			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Oesophageal spasm			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Pancreatitis			
subjects affected / exposed	1 / 554 (0.18%)	2 / 552 (0.36%)	0 / 550 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Pancreatitis chronic			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Peritoneal haemorrhage			

subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Rectal haemorrhage			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	2 / 550 (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
Salivary gland calculus			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Umbilical hernia			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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 / 554 (0.00%)	0 / 552 (0.00%)	2 / 550 (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
Cholelithiasis			

subjects affected / exposed	2 / 554 (0.36%)	0 / 552 (0.00%)	1 / 550 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatomyositis			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Erythema nodosum			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Psoriasis			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Skin laxity			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Gouty arthritis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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

Intervertebral disc degeneration			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Intervertebral disc protrusion			
subjects affected / exposed	1 / 554 (0.18%)	1 / 552 (0.18%)	1 / 550 (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
Lumbar spinal stenosis			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Osteonecrosis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	1 / 550 (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
Spinal osteoarthritis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	1 / 550 (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
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Appendicitis			

subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Arthritis bacterial			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Atypical mycobacterial infection			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Atypical mycobacterial lower respiratory tract infection			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Bronchitis			
subjects affected / exposed	1 / 554 (0.18%)	3 / 552 (0.54%)	3 / 550 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Cellulitis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Cellulitis pharyngeal			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Cystitis			

subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Disseminated tuberculosis			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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	0 / 554 (0.00%)	0 / 552 (0.00%)	2 / 550 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Infectious pleural effusion			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Periorbital cellulitis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	1 / 550 (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
Peritonsillar abscess			

subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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	22 / 554 (3.97%)	18 / 552 (3.26%)	16 / 550 (2.91%)
occurrences causally related to treatment / all	1 / 24	2 / 19	0 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	5 / 554 (0.90%)	8 / 552 (1.45%)	10 / 550 (1.82%)
occurrences causally related to treatment / all	0 / 5	0 / 9	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia haemophilus			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Pneumonia klebsiella			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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 moraxella			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Pneumonia necrotising			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Pneumonia pneumococcal			
subjects affected / exposed	2 / 554 (0.36%)	0 / 552 (0.00%)	1 / 550 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pseudomonal			

subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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 streptococcal			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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 viral			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	1 / 550 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	1 / 550 (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
Pulmonary tuberculosis			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Rhinovirus infection			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	0 / 550 (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
Sepsis			
subjects affected / exposed	0 / 554 (0.00%)	2 / 552 (0.36%)	0 / 550 (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
Septic shock			

subjects affected / exposed	1 / 554 (0.18%)	1 / 552 (0.18%)	0 / 550 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	1 / 554 (0.18%)	0 / 552 (0.00%)	0 / 550 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	1 / 550 (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
Urinary tract infection			
subjects affected / exposed	2 / 554 (0.36%)	2 / 552 (0.36%)	0 / 550 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	2 / 550 (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
Diabetes mellitus			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Hyperglycaemia			
subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	1 / 550 (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
Hypoglycaemia			
subjects affected / exposed	0 / 554 (0.00%)	0 / 552 (0.00%)	1 / 550 (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
Hyponatraemia			

subjects affected / exposed	0 / 554 (0.00%)	1 / 552 (0.18%)	1 / 550 (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 / 0

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

Non-serious adverse events	Benralizumab 30 mg	Benralizumab 100 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	401 / 554 (72.38%)	427 / 552 (77.36%)	390 / 550 (70.91%)
Vascular disorders			
Hypertension			
subjects affected / exposed	19 / 554 (3.43%)	19 / 552 (3.44%)	18 / 550 (3.27%)
occurrences (all)	19	19	19
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 554 (3.79%)	26 / 552 (4.71%)	20 / 550 (3.64%)
occurrences (all)	29	30	21
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	11 / 554 (1.99%)	26 / 552 (4.71%)	11 / 550 (2.00%)
occurrences (all)	13	28	11
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	17 / 554 (3.07%)	19 / 552 (3.44%)	15 / 550 (2.73%)
occurrences (all)	19	19	17
Diarrhoea			
subjects affected / exposed	17 / 554 (3.07%)	15 / 552 (2.72%)	6 / 550 (1.09%)
occurrences (all)	18	18	7
Nausea			
subjects affected / exposed	13 / 554 (2.35%)	18 / 552 (3.26%)	13 / 550 (2.36%)
occurrences (all)	17	22	15
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	16 / 554 (2.89%)	14 / 552 (2.54%)	21 / 550 (3.82%)
occurrences (all)	18	20	30
Dyspnoea			

subjects affected / exposed	24 / 554 (4.33%)	17 / 552 (3.08%)	23 / 550 (4.18%)
occurrences (all)	30	19	37
Oropharyngeal pain			
subjects affected / exposed	14 / 554 (2.53%)	18 / 552 (3.26%)	13 / 550 (2.36%)
occurrences (all)	15	21	17
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	21 / 554 (3.79%)	25 / 552 (4.53%)	19 / 550 (3.45%)
occurrences (all)	23	30	19
Infections and infestations			
Bronchitis			
subjects affected / exposed	59 / 554 (10.65%)	84 / 552 (15.22%)	80 / 550 (14.55%)
occurrences (all)	74	113	121
Lower respiratory tract infection			
subjects affected / exposed	50 / 554 (9.03%)	32 / 552 (5.80%)	29 / 550 (5.27%)
occurrences (all)	76	47	39
Oral candidiasis			
subjects affected / exposed	17 / 554 (3.07%)	13 / 552 (2.36%)	15 / 550 (2.73%)
occurrences (all)	21	18	16
Respiratory tract infection			
subjects affected / exposed	10 / 554 (1.81%)	11 / 552 (1.99%)	18 / 550 (3.27%)
occurrences (all)	10	14	26
Respiratory tract infection viral			
subjects affected / exposed	15 / 554 (2.71%)	12 / 552 (2.17%)	19 / 550 (3.45%)
occurrences (all)	21	18	23
Sinusitis			
subjects affected / exposed	13 / 554 (2.35%)	17 / 552 (3.08%)	20 / 550 (3.64%)
occurrences (all)	16	22	22
Upper respiratory tract infection			
subjects affected / exposed	69 / 554 (12.45%)	74 / 552 (13.41%)	65 / 550 (11.82%)
occurrences (all)	87	104	97
Urinary tract infection			
subjects affected / exposed	23 / 554 (4.15%)	22 / 552 (3.99%)	15 / 550 (2.73%)
occurrences (all)	27	30	22
Viral upper respiratory tract infection			

subjects affected / exposed occurrences (all)	83 / 554 (14.98%) 126	95 / 552 (17.21%) 134	66 / 550 (12.00%) 98

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 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
27 January 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