Clinical trial results:
A multicentre, randomised, double-blind, parallel group, placebo-controlled, Phase III efficacy and safety study of benralizumab (MEDI-563) added to high-dose inhaled corticosteroid plus long-acting beta2 agonist in patients with uncontrolled asthma (SIROCCO)

Summary

EudraCT number	2013-002345-11
Trial protocol	IT GB CZ ES BG PL
Global end of trial date	11 May 2016

Results information

Result version number	v1 (current)
This version publication date	14 October 2016
First version publication date	14 October 2016

Trial information

Trial identification

Sponsor protocol code	D3250C00017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01928771
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Vastra Malarehamnen 9, Sodertalje, Sweden, 151 85
Public contact	Mitchell Goldman, AstraZeneca AB, Mitchell.Goldman@astrazeneca.com
Scientific contact	AZ Clinical Study Information, AstraZeneca AB, 46 855 326000, information.center@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001214-PIP01-11
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	11 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 May 2016
Global end of trial reached?	Yes
Global end of trial date	11 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the effect of two dosing regimens of benralizumab on asthma exacerbations in patients on high-dose ICS-LABA with uncontrolled asthma

Protection of trial subjects:

Data safety monitoring board (DSMB) evaluates cumulative safety and other clinical trial data at regular intervals and making appropriate recommendations based on the available data. The DSMB functions independently of all other individuals associated with the conduct of the studies, including the study sponsor, AstraZeneca. The committee operates in accordance with a DSMB charter.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 September 2013
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	Australia: 45
Country: Number of subjects enrolled	Brazil: 36
Country: Number of subjects enrolled	Bulgaria: 110
Country: Number of subjects enrolled	Czech Republic: 47
Country: Number of subjects enrolled	France: 91
Country: Number of subjects enrolled	Italy: 45
Country: Number of subjects enrolled	Mexico: 21
Country: Number of subjects enrolled	Peru: 97
Country: Number of subjects enrolled	Poland: 75
Country: Number of subjects enrolled	Russian Federation: 155
Country: Number of subjects enrolled	South Africa: 26
Country: Number of subjects enrolled	Korea, Republic of: 122
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	Turkey: 42
Country: Number of subjects enrolled	United Kingdom: 38
Country: Number of subjects enrolled	United States: 203
Country: Number of subjects enrolled	Vietnam: 15
Worldwide total number of subjects	1204
EEA total number of subjects	442

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)	53
Adults (18-64 years)	1008
From 65 to 84 years	143
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

1205 participants were randomised to receive treatment with benralizumab 30 mg Q4W, Q8W, or placebo. Of the 1205 patients randomised, 1204 (99.9%) patients received treatment with the study drug: 399 patients received benralizumab 30 mg Q4W, 398 patients received benralizumab 30 mg Q8W, and 407 patients received 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 q.4 weeks

Arm description:

Benralizumab administered every 4 weeks 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 30 mg q.8 weeks

Arm description:

Benralizumab administered every 8 weeks 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	Placebo

Arm description:

Placebo administered subcutaneously

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in cartridge
Routes of administration	Subcutaneous use

Dosage and administration details:
30 mg

Number of subjects in period 1	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo
Started	399	398	407
Completed	354	358	367
Not completed	45	40	40
Adverse event, serious fatal	2	2	2
Consent withdrawn by subject	20	15	17
Severe Non-Compliance to Protocol	4	2	2
Adverse event, non-fatal	6	5	1
Other Reasons	9	9	14
Lost to follow-up	4	6	3
Study-Specific Withdrawal Criteria	-	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Benralizumab 30 mg q.4 weeks
Reporting group description:	
Benralizumab administered every 4 weeks subcutaneously.	
Reporting group title	Benralizumab 30 mg q.8 weeks
Reporting group description:	
Benralizumab administered every 8 weeks subcutaneously.	
Reporting group title	Placebo
Reporting group description:	
Placebo administered subcutaneously	

Reporting group values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo
Number of subjects	399	398	407
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	11	19	23
Adults (18-64 years)	338	339	331
From 65-84 years	50	40	53
85 years and over	0	0	0
Age Continuous | Units: Years			
arithmetic mean	50.1	47.6	48.7
standard deviation	± 13.4	± 14.5	± 14.9
Gender, Male/Female Units: Participants			
Female	275	252	269
Male	124	146	138

Reporting group values	Total		
Number of subjects	1204		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	53		
Adults (18-64 years)	1008		

From 65-84 years	143		
85 years and over	0		

Age Continuous |			
Units: Years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: Participants			
Female	796		
Male	408		

End points

End points reporting groups

Reporting group title	Benralizumab 30 mg q.4 weeks
Reporting group description:	
Benralizumab administered every 4 weeks subcutaneously.	
Reporting group title	Benralizumab 30 mg q.8 weeks
Reporting group description:	
Benralizumab administered every 8 weeks subcutaneously.	
Reporting group title	Placebo
Reporting group description:	
Placebo administered subcutaneously	

Primary: Annual asthma exacerbation rate in adult and adolescent patients with uncontrolled asthma for baseline eosinophils >=300/uL

End point title	Annual asthma exacerbation rate in adult and adolescent patients with uncontrolled asthma for baseline eosinophils >=300/uL
End point description:	
The annual exacerbation rate is based on unadjudicated annual exacerbation rate reported by the investigator in the eCRF. The analysis is based on the primary population, ie, baseline eosinophils >=300/uL	
End point type	Primary
End point timeframe:	
Immediately following the first administration of study drug through Study Week 48.	

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	275	267	267	
Units: Rate of event over follow-up time				
least squares mean (confidence interval 95%)	0.73 (0.6 to 0.89)	0.65 (0.53 to 0.8)	1.33 (1.12 to 1.58)	

Statistical analyses

Statistical analysis title	Negative binomial analysis
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo

Number of subjects included in analysis	542
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.71

Statistical analysis title	Negative binomial analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.64

Secondary: Annual asthma exacerbation rate resulting emergency room visits and hospitalizations

End point title	Annual asthma exacerbation rate resulting emergency room visits and hospitalizations

End point description:

The annual exacerbation rate associated with an emergency room visit or a hospitalization (adjudicated). This analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study Week 48.

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	275	267	267	
Units: Rate of event over follow-up time				
least squares mean (confidence interval 95%)	0.11 (0.07 to 0.16)	0.06 (0.04 to 0.11)	0.18 (0.13 to 0.25)	

Statistical analyses

Statistical analysis title	Negative binomial analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.67

Statistical analysis title	Negative binomial analysis
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	542
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.053
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	1.01

Secondary: Proportion of patients with >=1 asthma exacerbations and time to first asthma exacerbation

End point title	Proportion of patients with >=1 asthma exacerbations and time to first asthma exacerbation

End point description: Analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL	
End point type	Secondary
End point timeframe: Immediately following the first administration of study drug through Study Week 48.	

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	275	267	267	
Units: Count	100	93	135	

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel test
Statistical analysis description: Proportion of patients with >=1 asthma exacerbation	
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	542
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.78

Statistical analysis title	Cochran-Mantel-Haenszel test
Statistical analysis description: Proportion of patients with >=1 asthma exacerbation	
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.9

Statistical analysis title	Time to event analysis
Statistical analysis description: Time to first exacerbation	
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	542
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.82

Statistical analysis title	Time to event analysis
Statistical analysis description: Time to first exacerbation	
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.78

Secondary: Mean change from baseline to Week 48 in pre-bronchodilator FEV1 (L) value for patients with baseline eosinophils >=300/uL

End point title	Mean change from baseline to Week 48 in pre-bronchodilator FEV1 (L) value for patients with baseline eosinophils >=300/uL

End point description:	
Analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL	
End point type	Secondary
End point timeframe:	
Immediately following the first administration of study drug through Study Week 48.	

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	275	267	267	
Units: Liter				
arithmetic mean (standard deviation)	0.353 (± 0.503)	0.398 (± 0.546)	0.237 (± 0.508)	

Statistical analyses

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.159
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.068
upper limit	0.249

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	542
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.106

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.016
upper limit	0.196

Secondary: Mean change from baseline to Week 48 in asthma symptom score for patients with baseline eosinophils >=300/uL

End point title	Mean change from baseline to Week 48 in asthma symptom score for patients with baseline eosinophils >=300/uL

End point description:

Asthma symptoms during night time and day time are recorded by the patient each morning and evening in the asthma daily diary. Baseline is defined as the average of data collected from the evening of study day -10 to the morning of study day 1. Each time point is calculated as bi-weekly means based on daily diary data. If more than 50% of scores are missing in a 14 day period then this is considered as missing. Symptom score lower is better. Analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL.

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study Week 48.

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	275	267	267	
Units: Scale of score				
arithmetic mean (standard deviation)	-1.15 (± 1.31)	-1.34 (± 1.27)	-1.03 (± 1.07)	

Statistical analyses

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	-0.06

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	542
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.442
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.12

Secondary: Change in asthma rescue medication

End point title	Change in asthma rescue medication

End point description:

Change from baseline to week 48 in number of rescue medication use (puffs/day). Analysis is based on primary analysis population, ie, baseline eosinophils >=300/uL

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study Week 48.

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	275	267	267	
Units: Puffs/day				
arithmetic mean (standard deviation)	-2.74 (± 4.29)	-2.78 (± 3.9)	-2.18 (± 4.38)	

Statistical analyses

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo

Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.081
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.21
upper limit	0.07

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	542
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.16
upper limit	0.1

Secondary: Home lung function assessment based on PEF

End point title	Home lung function assessment based on PEF

End point description:

Change from baseline to week 48 in home lung function (morning and evening peak expiratory flow [PEF]). Analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL.

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study Week 48.

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	275	267	267	
Units: L/min				
arithmetic mean (standard deviation)				

Morning at Week 48 (n=205, 181, 189)	45.857 (± 84.227)	36.994 (± 72.002)	22.059 (± 74.434)	
Evening at Week 48 (n=203, 187, 189)	36.806 (± 86.271)	33.46 (± 74.017)	14.784 (± 68.799)	

Statistical analyses

Statistical analysis title	Mix effect repeated measurement analysis
Statistical analysis description:	
Morning PEF change from baseline to Week 48	
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	542
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	23.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.2
upper limit	37.43

Statistical analysis title	Mix effect repeated measurement analysis
Statistical analysis description:	
Morning PEF change from baseline to Week 48	
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	16.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.08
upper limit	30.83

Statistical analysis title	Mix effect repeated measurement analysis
Statistical analysis description:	
Evening PEF change from baseline to Week 48	
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo

Number of subjects included in analysis	542
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	21.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.86
upper limit	35.65

Statistical analysis title	Mix effect repeated measurement analysis
Statistical analysis description:	
Evening PEF change from baseline to Week 48	
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	19.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.09
upper limit	33.28

Secondary: Proportion of night awakening due to asthma

End point title	Proportion of night awakening due to asthma
End point description:	
Change from baseline to Week 48 on proportion of night awakening due to asthma. Analysis is based on primary analysis population, ie, baseline eosinophils >=300/uL.	
End point type	Secondary
End point timeframe:	
Immediately following the first administration of study drug through Study Week 48.	

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	275	267	267	
Units: Proportion				
arithmetic mean (standard deviation)	-0.314 (± 0.366)	-0.38 (± 0.385)	-0.26 (± 0.344)	

Statistical analyses

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	-0.01

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	542
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.964
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.04

Secondary: Mean change from baseline to Week 48 in ACQ-6 for patients with baseline eosinophils >=300/uL

End point title	Mean change from baseline to Week 48 in ACQ-6 for patients with baseline eosinophils >=300/uL

End point description:

ACQ-6 contains one bronchodilator question and 5 symptom questions. Questions are rated from 0 (totally controlled) to 6 (severely uncontrolled). Mean ACQ-6 score is the average of the responses. Mean scores of <=0.75 indicates well-controlled asthma, scores between 0.75 to <=1.5 indicate partly controlled asthma, and >1.5 indicates not well controlled asthma. Analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL.

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study Week 48.

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	275	267	267	
Units: Scale of score				
arithmetic mean (standard deviation)	-1.33 (± 1.18)	-1.47 (± 1.05)	-1.12 (± 1.15)	

Statistical analyses

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	-0.1

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	542
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.111
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	0.04

Secondary: Pharmacokinetics of benralizumab

End point title	Pharmacokinetics of benralizumab

End point description:

Mean PK concentrations at each visit

End point type	Secondary

End point timeframe:

Baseline, week 4, week 4 day 6, week 8, week 16, week 24, week 32, week 40, week 48, week 56

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	399	391	0[1]	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Baseline (n=395, 386)	0 (± 0)	0 (± 0)	()	
Week 4 (n=393, 375)	632.84 (± 152.14)	629.89 (± 169.22)	()	
Week 4 day 6 (n=54, 63)	1368.98 (± 633.33)	1273.7 (± 688.2)	()	
Week 8 (n=377, 366)	916.25 (± 142.53)	881.57 (± 156.12)	()	
Week 16 (n=358, 350)	1024.26 (± 174.08)	250.84 (± 228.25)	()	
Week 24 (n=349, 344)	926.62 (± 231.75)	184.08 (± 298.92)	()	
Week 32 (n=260, 267)	853.67 (± 248.6)	152.73 (± 394.18)	()	
Week 40 (n=328, 333)	967.15 (± 218.32)	157.22 (± 364.6)	()	
Week 48 (n=333, 333)	864.37 (± 283.87)	162.51 (± 352.46)	()	
Week 56 (n=63, 67)	51.7 (± 833.91)	6.66 (± 321.88)	()	

Notes:

[1] - Not applicable since it is not experimental product

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity of benralizumab

End point title	Immunogenicity of benralizumab

End point description:

Anti-drug antibodies (ADA) responses at baseline and post baseline. Persistently positive is defined as positive at >=2 post baseline assessments (with >=16 weeks between the first and the last positive) or positive at last post baseline assessment. Transiently positive is defined as having at least one post baseline ADA positive assessment and not fulfilling the conditions of persistently positive.

End point type	Secondary

End point timeframe:

Pre-treatment until end of follow-up

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	399[2]	394	407	
Units: Count				
Positive at any visit	47	58	21	
Baseline and >=1 post baseline result available	393	381	396	
Both baseline and post baseline positive	2	3	10	
>=1 post baseline result available	396	389	402	
Only post baseline positive	39	49	10	
Persistently positive	23	39	16	
Transiently positive	18	13	4	
Baseline result available	399	385	401	
Only baseline positive	6	6	1	

Notes:

[2] - 4 patients randomized to q8, but treated with q4, so 403 in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Extend of exposure

End point title	Extend of exposure

End point description:

Extend of exposure is defined as duration of treatment in days

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study Week 48.

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	399[3]	394	407	
Units: Days				
arithmetic mean (standard deviation)	285.86 (± 67.446)	288.02 (± 66.683)	289.38 (± 61.527)	

Notes:

[3] - 4 patients randomized to q8, but treated q4, so 403 in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline to week 48 in AQLQ(S)+12

End point title	Mean change from baseline to week 48 in AQLQ(S)+12

End point description:

AQLQ(S)+12 overall score is defined as the average of all 32 questions in the AQLQ(S)+12 questionnaire. AQLQ(S)+12 is a 7-point scale questionnaire, ranging from 7 (no impairment) to 1 (severe impairment). Total or domain score change of >=0.5 are considered clinically meaningful. Analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL.

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study Week 48.

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	275	267	267	
Units: Scale of score				
arithmetic mean (standard deviation)	1.44 (± 1.18)	1.56 (± 1.17)	1.25 (± 1.18)	

Statistical analyses

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	542
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.081
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.37

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.5

Secondary: Mean change from baseline to week 48 in EQ-5D-5L VAS

End point title	Mean change from baseline to week 48 in EQ-5D-5L VAS

End point description:

EQ-5D-5L VAS is to rate current health status on a scale of 0-100, with 0 being the worst imaginable health state. Analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL.

End point type	Secondary

End point timeframe:

Week 48

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191	186	181	
Units: Scale of score				
arithmetic mean (standard deviation)	13.5 (± 21.82)	16.5 (± 23.66)	12.5 (± 21.41)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean work productivity loss due to asthma

End point title	Mean work productivity loss due to asthma

End point description:

WPAI+CIQ work productivity loss at Week 48. Analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL, and also only patients who were employed are applicable.

End point type	Secondary

End point timeframe:

Week 48

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	79	76	
Units: Percent				
arithmetic mean (standard deviation)	23.31 (± 24.169)	26.11 (± 23.06)	35.36 (± 24.537)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean productivity loss due to asthma in classroom

End point title	Mean productivity loss due to asthma in classroom

End point description:

WPAI+CIQ productivity loss at Week 48 in classroom. Analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL, and also only patients who attended classes are applicable.

End point type	Secondary

End point timeframe:

Week 48

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	6	18	
Units: Percent				
arithmetic mean (standard deviation)	30.97 (± 25.311)	27.17 (± 38.456)	49.1 (± 25.801)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of healthcare utilization

End point title	Number of healthcare utilization

End point description:

Analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL.

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study Week 48.

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	275	267	267	
Units: Count				
Hospitalizations	14	12	20	
Emergency department visits	20	10	26	
Unscheduled outpatient visits	77	87	109	
Home visits	2	1	3	
Telephone calls	46	41	62	
Ambulance transports	6	3	9	

Statistical analyses

No statistical analyses for this end point

Secondary: Patient and clinician's responder assessment to treatment

End point title	Patient and clinician's responder assessment to treatment

End point description:

CGIC (Clinical global impression of change), and PGIC (Patient global impression of change) are overall evaluation of response to treatment, conducted separately by investigator and patient using 7-point rating scale, ranging from 1 (very much improved), to 7 (very much worse). Analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL. Due to the measurement was added after the second amendment of the protocol, not all patients had data for the analyses.

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study Week 48

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	275	267	267	
Units: Count				
CGIC improved	80	76	88	
CGIC much improved	59	58	58	
CGIC very much improved	18	12	5	
CGIC total responder	157	146	151	
PGIC improved	84	80	91	

PGIC much improved	55	58	65	
PGIC very much improved	26	19	11	
PGIC total responder	165	157	167	

Statistical analyses

No statistical analyses for this end point

Secondary: Annual asthma exacerbation rate in adult and adolescent patients with uncontrolled asthma for baseline eosinophils <300/uL

End point title	Annual asthma exacerbation rate in adult and adolescent patients with uncontrolled asthma for baseline eosinophils <300/uL

End point description:

The annual exacerbation rate is based on unadjudicated annual exacerbation rate reported by the investigator in the eCRF. The analysis based on patients with baseline eosinophils <300/uL.

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study Week 48.

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124	131	140	
Units: Rate of event over follow-up time				
least squares mean (confidence interval 95%)	0.85 (0.65 to 1.11)	1 (0.78 to 1.28)	1.21 (0.96 to 1.52)	

Statistical analyses

Statistical analysis title	Negative binomial analysis
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047
Method	Negative binomial
Parameter estimate	rate ratio
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1

Statistical analysis title	Negative binomial analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.268
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.16

Secondary: Mean change from baseline to Week 48 in pre-bronchodilator FEV1 (L) value for patients with baseline eosinophils <300/uL

End point title	Mean change from baseline to Week 48 in pre-bronchodilator FEV1 (L) value for patients with baseline eosinophils <300/uL

End point description:

Analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study Week 48.

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124	131	140	
Units: Liter				
arithmetic mean (standard deviation)	0.115 (± 0.417)	0.238 (± 0.483)	0.14 (± 0.4)	

Statistical analyses

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo

Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.644
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.025
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.134
upper limit	0.083

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.057
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.102
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.003
upper limit	0.208

Secondary: Mean change from baseline to Week 48 in asthma symptom score for patients with baseline eosinophils <300/uL

End point title	Mean change from baseline to Week 48 in asthma symptom score for patients with baseline eosinophils <300/uL

End point description:

Asthma symptoms during night time and day time are recorded by the patient each morning and evening in the asthma daily diary. Baseline is defined as the average of data collected from the evening of study day -10 to the morning of study day 1. Each time point is calculated as bi-weekly means based on daily diary data. If more than 50% of scores are missing in a 14 day period then this is considered as missing. Symptom score lower is better. Analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL.

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study Week 48.

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124	131	140	
Units: Scale of score				
arithmetic mean (standard deviation)	-0.98 (± 1.19)	-1.04 (± 1.24)	-0.78 (± 0.99)	

Statistical analyses

Statistical analysis title	Mix effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.169
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	0.08

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	-0.01

Secondary: Mean change from baseline to Week 48 in ACQ-6 for patients with baseline eosinophils <300/uL

End point title	Mean change from baseline to Week 48 in ACQ-6 for patients with baseline eosinophils <300/uL

End point description:

ACQ-6 contains one bronchodilator question and 5 symptom questions. Questions are rated from 0 (totally controlled) to 6 (severely uncontrolled). Mean ACQ-6 score is the average of the responses. Mean scores of <=0.75 indicates well-controlled asthma, scores between 0.75 to <=1.5 indicate partly controlled asthma, and >1.5 indicates not well controlled asthma. Analysis is based on the primary analysis population, ie, baseline eosinophils <300/uL.

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study Week 48.

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124	131	140	
Units: Scale of score				
arithmetic mean (standard deviation)	-0.77 (± 1.07)	-1.14 (± 1.11)	-0.89 (± 1.01)	

Statistical analyses

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.99
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.27

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.107
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.22

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	0.05

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall study period	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Benralizumab 30 mg q.4 weeks
Reporting group description:	
Benralizumab administered every 4 weeks subcutaneously.	
Reporting group title	Placebo
Reporting group description:	
Placebo administered subcutaneously	
Reporting group title	Benralizumab 30 mg q.8 weeks
Reporting group description:	
Benralizumab administered every 8 weeks subcutaneously.	

Serious adverse events	Benralizumab 30 mg q.4 weeks	Placebo	Benralizumab 30 mg q.8 weeks
Total subjects affected by serious adverse events			
subjects affected / exposed	51 / 403 (12.66%)	58 / 407 (14.25%)	54 / 394 (13.71%)
number of deaths (all causes)	2	2	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenolymphoma			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon adenoma			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ovarian epithelial cancer			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (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 disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 403 (0.00%)	1 / 407 (0.25%)	0 / 394 (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
Hypertension			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	2 / 394 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 403 (0.00%)	1 / 407 (0.25%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 403 (0.00%)	1 / 407 (0.25%)	0 / 394 (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
Injection site erythema			
subjects affected / exposed	0 / 403 (0.00%)	1 / 407 (0.25%)	0 / 394 (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
Oedema peripheral			

subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (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 death			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Immune system disorders			
Allergic granulomatous angiitis			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contrast media allergy			
subjects affected / exposed	0 / 403 (0.00%)	1 / 407 (0.25%)	0 / 394 (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			
Endometriosis			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (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
Asthma			
subjects affected / exposed	23 / 403 (5.71%)	32 / 407 (7.86%)	24 / 394 (6.09%)
occurrences causally related to treatment / all	0 / 29	0 / 42	0 / 33
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nasal polyps			

subjects affected / exposed	2 / 403 (0.50%)	1 / 407 (0.25%)	0 / 394 (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
Pulmonary embolism			
subjects affected / exposed	1 / 403 (0.25%)	2 / 407 (0.49%)	0 / 394 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sinus polyp			
subjects affected / exposed	0 / 403 (0.00%)	1 / 407 (0.25%)	0 / 394 (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 / 403 (0.00%)	1 / 407 (0.25%)	0 / 394 (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
Panic attack			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (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	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 403 (0.00%)	1 / 407 (0.25%)	0 / 394 (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

Femoral neck fracture			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (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
Ligament sprain			
subjects affected / exposed	0 / 403 (0.00%)	1 / 407 (0.25%)	0 / 394 (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
Incisional hernia			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 403 (0.00%)	1 / 407 (0.25%)	0 / 394 (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 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle rupture			
subjects affected / exposed	0 / 403 (0.00%)	1 / 407 (0.25%)	0 / 394 (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
Overdose			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Post procedural complication			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (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
Procedural complication			

subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
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 / 403 (0.00%)	1 / 407 (0.25%)	0 / 394 (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
Tendon rupture			
subjects affected / exposed	0 / 403 (0.00%)	1 / 407 (0.25%)	0 / 394 (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 myocardial infarction			
subjects affected / exposed	1 / 403 (0.25%)	1 / 407 (0.25%)	0 / 394 (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
Angina unstable			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
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	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (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
Nervous system disorders			

Aphonia			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (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
Cerebral haemorrhage			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (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
Cerebral venous thrombosis			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Hypercoagulation			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (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
Optic nerve disorder			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (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			
Gastric ulcer			

subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (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
Gastritis			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	0 / 403 (0.00%)	1 / 407 (0.25%)	0 / 394 (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
Inguinal hernia			
subjects affected / exposed	0 / 403 (0.00%)	1 / 407 (0.25%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
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	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (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
Volvulus			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
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 acute			

subjects affected / exposed	2 / 403 (0.50%)	1 / 407 (0.25%)	0 / 394 (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
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (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
Dermatitis atopic			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
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 / 403 (0.00%)	1 / 407 (0.25%)	0 / 394 (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
Rash papular			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria papular			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (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			
Nephrolithiasis			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (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 failure			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Goitre			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Foot deformity			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (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
Intervertebral disc degeneration			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	0 / 403 (0.00%)	1 / 407 (0.25%)	0 / 394 (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
Osteoarthritis			
subjects affected / exposed	1 / 403 (0.25%)	2 / 407 (0.49%)	0 / 394 (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
Spinal osteoarthritis			
subjects affected / exposed	0 / 403 (0.00%)	1 / 407 (0.25%)	0 / 394 (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
Vertebral foraminal stenosis			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
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 pneumonia			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (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
Bullous impetigo			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 403 (0.00%)	1 / 407 (0.25%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	2 / 403 (0.50%)	1 / 407 (0.25%)	0 / 394 (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
Otitis media			
subjects affected / exposed	0 / 403 (0.00%)	1 / 407 (0.25%)	0 / 394 (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
Parotitis			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
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	0 / 403 (0.00%)	3 / 407 (0.74%)	2 / 394 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
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 pneumococcal			
subjects affected / exposed	0 / 403 (0.00%)	1 / 407 (0.25%)	0 / 394 (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 viral			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (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
Pyelonephritis			
subjects affected / exposed	0 / 403 (0.00%)	1 / 407 (0.25%)	0 / 394 (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
Sinusitis			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 403 (0.00%)	2 / 407 (0.49%)	0 / 394 (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
Urinary tract infection enterococcal			

subjects affected / exposed	0 / 403 (0.00%)	1 / 407 (0.25%)	0 / 394 (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
Vestibular neuronitis			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 403 (0.25%)	0 / 407 (0.00%)	0 / 394 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 403 (0.00%)	0 / 407 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	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 q.4 weeks	Placebo	Benralizumab 30 mg q.8 weeks
Total subjects affected by non-serious adverse events			
subjects affected / exposed	214 / 403 (53.10%)	219 / 407 (53.81%)	199 / 394 (50.51%)
Nervous system disorders			
Headache			
subjects affected / exposed	31 / 403 (7.69%)	21 / 407 (5.16%)	37 / 394 (9.39%)
occurrences (all)	38	28	61
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	16 / 403 (3.97%)	8 / 407 (1.97%)	12 / 394 (3.05%)
occurrences (all)	21	8	19
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	8 / 403 (1.99%)	8 / 407 (1.97%)	12 / 394 (3.05%)
occurrences (all)	12	9	14
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	15 / 403 (3.72%)	11 / 407 (2.70%)	13 / 394 (3.30%)
occurrences (all)	17	15	14
Asthma			
subjects affected / exposed	48 / 403 (11.91%)	60 / 407 (14.74%)	27 / 394 (6.85%)
occurrences (all)	64	102	38
Rhinitis allergic			
subjects affected / exposed	11 / 403 (2.73%)	8 / 407 (1.97%)	12 / 394 (3.05%)
occurrences (all)	11	9	12
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 403 (2.73%)	12 / 407 (2.95%)	18 / 394 (4.57%)
occurrences (all)	13	19	20
Pain in extremity			
subjects affected / exposed	3 / 403 (0.74%)	5 / 407 (1.23%)	13 / 394 (3.30%)
occurrences (all)	3	6	13
Back pain			
subjects affected / exposed	12 / 403 (2.98%)	15 / 407 (3.69%)	8 / 394 (2.03%)
occurrences (all)	13	15	9
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	10 / 403 (2.48%)	11 / 407 (2.70%)	13 / 394 (3.30%)
occurrences (all)	11	15	14
Bronchitis			
subjects affected / exposed	27 / 403 (6.70%)	30 / 407 (7.37%)	19 / 394 (4.82%)
occurrences (all)	28	41	22
Gastroenteritis			
subjects affected / exposed	10 / 403 (2.48%)	6 / 407 (1.47%)	12 / 394 (3.05%)
occurrences (all)	16	6	14
Nasopharyngitis			
subjects affected / exposed	47 / 403 (11.66%)	49 / 407 (12.04%)	47 / 394 (11.93%)
occurrences (all)	62	64	69
Influenza			
subjects affected / exposed	15 / 403 (3.72%)	23 / 407 (5.65%)	19 / 394 (4.82%)
occurrences (all)	19	31	21
Pharyngitis			

subjects affected / exposed	17 / 403 (4.22%)	14 / 407 (3.44%)	23 / 394 (5.84%)
occurrences (all)	21	20	24
Sinusitis			
subjects affected / exposed	18 / 403 (4.47%)	29 / 407 (7.13%)	22 / 394 (5.58%)
occurrences (all)	23	43	34
Rhinitis			
subjects affected / exposed	16 / 403 (3.97%)	15 / 407 (3.69%)	10 / 394 (2.54%)
occurrences (all)	17	17	11
Upper respiratory tract infection			
subjects affected / exposed	45 / 403 (11.17%)	37 / 407 (9.09%)	32 / 394 (8.12%)
occurrences (all)	74	73	51

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2014	addition of adolescent patient population, amended incl/exclusion criteria, additional lab measurements
23 April 2015	addition of PRO questionaries, addition of MACE/Malignancies Adjudication, additional laboratory mesurments

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported