Clinical trial results:
A multicentre, randomised, double-blind, parallel group, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of benralizumab in asthmatic adults and adolescents inadequately controlled on inhaled corticosteroid plus long-acting beta2 agonist (CALIMA)

Summary

EudraCT number	2013-002163-26
Trial protocol	DE SE PL
Global end of trial date	04 May 2016

Results information

Result version number	v1
This version publication date	24 September 2016
First version publication date	24 September 2016

Trial information

Trial identification

Sponsor protocol code	D3250C00018

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01914757
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, 46 855 326000, information.center@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	04 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 May 2016
Global end of trial reached?	Yes
Global end of trial date	04 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	21 August 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	Argentina: 269
Country: Number of subjects enrolled	Canada: 59
Country: Number of subjects enrolled	Chile: 31
Country: Number of subjects enrolled	Germany: 159
Country: Number of subjects enrolled	Japan: 83
Country: Number of subjects enrolled	Poland: 290
Country: Number of subjects enrolled	Romania: 55
Country: Number of subjects enrolled	Sweden: 10
Country: Number of subjects enrolled	Ukraine: 118
Country: Number of subjects enrolled	United States: 171
Country: Number of subjects enrolled	Philippines: 61
Worldwide total number of subjects	1306
EEA total number of subjects	514

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)	55
Adults (18-64 years)	1074
From 65 to 84 years	177
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

1306 participants were randomised to receive treatment with benralizumab 30 mg Q4W, Q8W, or placebo. Of the 1306 patients randomised, all (100.0%) received treatment with study drug: 425 patients received benralizumab 30 mg Q4W, 441 patients received benralizumab 30 mg Q8W, and 440 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	Investigator, Monitor, Subject, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Benralizumab 30 mg q.4 weeks

Arm description:

Benralizumab administered subcutaneously every 4 weeks.

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 subcutaneously every 8 weeks.

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 pre-filled syringe
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	425	441	440
Completed	389	390	402
Not completed	36	51	38
Severe non-compliance to protocol	3	1	2
Adverse event, serious fatal	2	2	1
Consent withdrawn by subject	15	27	19
Eligibility criteria not fulfilled	2	-	2
Adverse event, non-fatal	4	3	4
Other reasons	5	9	4
Lost to follow-up	5	8	6
Study specific withdrawal criteria	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Benralizumab 30 mg q.4 weeks
Reporting group description:	
Benralizumab administered subcutaneously every 4 weeks.	
Reporting group title	Benralizumab 30 mg q.8 weeks
Reporting group description:	
Benralizumab administered subcutaneously every 8 weeks.	
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	425	441	440
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	21	23
Adults (18-64 years)	359	365	350
From 65-84 years	55	55	67
85 years and over	0	0	0
Age Continuous | Units: Years			
arithmetic mean	50	49	48.8
standard deviation	± 13.6	± 14.3	± 15.1
Gender, Male/Female Units: Participants			
Female	270	273	264
Male	155	168	176

Reporting group values	Total		
Number of subjects	1306		
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)	55		
Adults (18-64 years)	1074		

From 65-84 years	177		
85 years and over	0		

Age Continuous |			
Units: Years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: Participants			
Female	807		
Male	499		

End points

End points reporting groups

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

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

End point title	Annual asthma exacerbation rate in adult and adolescent patients with uncontrolled asthma, 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 analysis population, ie, baseline eosinophils >=300/uL and high-dose ICS	
End point type	Primary
End point timeframe:	
Immediately following the first administration of study drug through Study 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	241	239	248	
Units: Rate of event over follow-up time				
least squares mean (confidence interval 95%)	0.6 (0.48 to 0.74)	0.66 (0.54 to 0.82)	0.93 (0.77 to 1.12)	

Statistical analyses

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

Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Negative Binomial
Parameter estimate	Rate Ratio
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.85

Statistical analysis title	Negative Binomial Model
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	Negative Binomial
Parameter estimate	Rate Ratio
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.95

Secondary: Mean change from baseline to Week 56 in Pre-bronchodilator FEV1 (L) value for patients with baseline eosinophils >=300/uL

End point title	Mean change from baseline to Week 56 in Pre-bronchodilator FEV1 (L) value for patients with baseline eosinophils >=300/uL

End point description:

The analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL and high-dose ICS

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study 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	241	239	248	
Units: Liter				
arithmetic mean (standard deviation)	0.34 (± 0.469)	0.332 (± 0.518)	0.206 (± 0.471)	

Statistical analyses

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.125
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.037
upper limit	0.213

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.116
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.028
upper limit	0.204

Secondary: Mean change from baseline to Week 56 asthma symptoms score for patients with baseline eosinophils >=300/uL

End point title	Mean change from baseline to Week 56 asthma symptoms score for patients with baseline eosinophils >=300/uL

End point description:

Asthma symptoms during night time and daytime 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 timepoint 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. The analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL and high-dose ICS.

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study 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	241	239	248	
Units: Scale of score				
arithmetic mean (standard deviation)	-1.33 (± 1.23)	-1.4 (± 1.17)	-1.2 (± 1.19)	

Statistical analyses

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.224
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.07

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.23

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	-0.04

Secondary: Change in asthma rescue medication use

End point title	Change in asthma rescue medication use

End point description:

Change from Baseline to Week 56 in number of Rescue medication use (puffs/day). The analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL and high-dose ICS. The analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL and high-dose ICS

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study 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	241	239	248	
Units: Puffs per day				
arithmetic mean (standard deviation)	-2 (± 3.64)	-2.92 (± 3.6)	-2.65 (± 9.57)	

Statistical analyses

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.603
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	0.99

Statistical analysis title	Mixed Effect Model Repeated Measurement

Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.209
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.29
upper limit	0.28

Secondary: Home lung function assessments based on PEF

End point title	Home lung function assessments based on PEF

End point description:

Change from Baseline to Week 56 in Home lung function (morning and evening Peak expiratory flow [PEF]). The analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL and high-dose ICS

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study 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	241	239	248	
Units: L/min				
arithmetic mean (standard deviation)				
Morning at Week 56 (n=194, 193, 197)	41.745 (± 78.534)	43.375 (± 91.865)	23.961 (± 71.509)	
Evening at Week 56 (n=194, 192, 197)	35.142 (± 75.489)	39.27 (± 89.772)	15.448 (± 78.341)	

Statistical analyses

Statistical analysis title	Mixed Effect Model Repeated Measurement

Statistical analysis description:

Morning PEF Change from Baseline to Week 56

Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo

Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	15.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.59
upper limit	30.12

Statistical analysis title	Mixed Effect Model Repeated Measurement
Statistical analysis description:	
Morning PEF Change from Baseline to Week 56	
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	15.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	29.64

Statistical analysis title	Mixed Effect Model Repeated Measurement
Statistical analysis description:	
Evening PEF Change from Baseline to Week 56	
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	17.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.07
upper limit	32

Statistical analysis title	Mixed Effect Model Repeated Measurement
Statistical analysis description:	
Evening PEF Change from Baseline to Week 56	
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	21.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.65
upper limit	35.79

Secondary: Proportion of Nights with awakening due to asthma	
End point title	Proportion of Nights with awakening due to asthma
End point description:	
Change from Baseline to Week 56 on Proportion of Nights with awakening due to asthma. The analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL and high-dose ICS	
End point type	Secondary
End point timeframe:	
Immediately following the first administration of study drug through Study 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	241	239	248	
Units: Scale of score				
arithmetic mean (standard deviation)	-0.373 (± 0.388)	-0.431 (± 0.4)	-0.372 (± 0.405)	

Statistical analyses

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo

Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.03

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.146
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.01

Secondary: Mean change from baseline to Week 56 in ACQ-6 for patients with baseline eosinophils >=300/uL

End point title	Mean change from baseline to Week 56 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. The analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL and high-dose ICS

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study 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	241	239	248	
Units: Scale of score				
arithmetic mean (standard deviation)	-1.34 (± 1.13)	-1.49 (± 1.13)	-1.21 (± 1.12)	

Statistical analyses

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	-0.01

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	-0.07

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

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

End point description:

The analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL and high-dose ICS

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study 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	241	239	248	
Units: Count	84	95	126	

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	489
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	0.69

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	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.65

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.95

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	489
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.8

Statistical analysis title	Time to Event Analysis
Statistical analysis description: Time to first asthma exacerbation	
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	0.95

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

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

End point description:

Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization (adjudicated). The analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL and high-dose ICS

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study 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	241	239	248	
Units: Rate of event over follow-up time				
least squares mean (confidence interval 95%)	0.04 (0.02 to 0.06)	0.05 (0.03 to 0.08)	0.04 (0.02 to 0.07)	

Statistical analyses

Statistical analysis title	Negative Bionomial
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.837
Method	negative binomial
Parameter estimate	Rate Ratio
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.82

Statistical analysis title	Negative Binomial
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.538
Method	negative binomial
Parameter estimate	Rate Ratio
Point estimate	1.23

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	2.35

Secondary: Pharmacokinetics of benralizumab

End point title	Pharmacokinetics of benralizumab

End point description:

Mean PK Concentration at each visit

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 8, Week 16, Week 24, Week 32, Week 40, Week 48, Week 56, Week 60

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	425[1]	424	0[2]	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Baseline (n=435, 419)	0 (± 0)	0 (± 0)	()	
Week 4 (n=430, 416)	650.04 (± 154.61)	703.16 (± 89.48)	()	
Week 8 (n=414, 395)	894.86 (± 148.91)	939.45 (± 98.99)	()	
Week 16 (n=390, 378)	936.43 (± 247.46)	252.54 (± 274.74)	()	
Week 24 (n=388, 361)	827.09 (± 370.64)	188.99 (± 308.38)	()	
Week 32 (n=345, 323)	823.21 (± 362.43)	166.53 (± 289.34)	()	
Week 40 (n=370, 338)	859.69 (± 364.28)	172.28 (± 298.6)	()	
Week 48 (n=355, 337)	888.09 (± 333.98)	186.5 (± 290.28)	()	
Week 56 (n=358, 344)	763.98 (± 309.18)	173.41 (± 235.86)	()	
Week 60 (n=49, 45)	53.63 (± 1782.96)	18.63 (± 756.47)	()	

Notes:

[1] - Patients were treated with q.4 weeks instead of q.8 weeks, so 435 in the analysis.

[2] - No concentration of 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 first and 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	425[3]	428	440	
Units: Count				
Positive at any visit	63	64	13	
Baseline and >=1 post-baseline result available	431	414	430	
Both baseline and post-baseline positive	5	5	5	
>=1 post-baseline result available	431	420	436	
Only post-baseline positive	55	57	8	
Persistently positive	44	42	7	
Transient positive	16	20	6	
Baseline result available	438	421	434	
Only baseline positive	3	2	0	

Notes:

[3] - Patients were treated with q.4 rather than q.8. So 438 in the analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Extent of exposure

End point title	Extent of exposure

End point description:

Extent of exposure is defined as the duration of treatment in days

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study 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	425[4]	428	440	
Units: Days				
arithmetic mean (standard deviation)	344.14 (± 73.129)	331.64 (± 88.839)	336.69 (± 82.148)	

Notes:

[4] - 13 more patients were treated with q.4 rather than q.8, so 438 in the analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline to Week 56 in AQLQ(S)+12

End point title	Mean change from baseline to Week 56 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. The analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL and high-dose ICS

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study 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	241	239	248	
Units: Scale of score				
arithmetic mean (standard deviation)	1.44 (± 1.15)	1.61 (± 1.24)	1.32 (± 1.19)	

Statistical analyses

Statistical analysis title	Mixed Effect Repeated Measurement
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.119
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.16

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.37

Statistical analysis title	Mixed Effect Repeated Measurement
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.45

Secondary: Change from baseline to Week 56 in EQ-5D-5L VAS	
End point title	Change from baseline to Week 56 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. The analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL and high-dose ICS	
End point type	Secondary
End point timeframe:	
Immediately following the first administration of study drug through Study 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	241	239	248	
Units: Scale of score				
arithmetic mean (standard deviation)	13.8 (± 21.52)	15.5 (± 20.36)	12.1 (± 20.13)	

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 56. The analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL and high-dose ICS, and is only applicable for patients employed.

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study 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	117	125	113	
Units: percent				
arithmetic mean (standard deviation)	26.56 (± 25.589)	24.44 (± 24.689)	27.29 (± 25.802)	

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 Class room productivity loss at Week 56. The analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL and high-dose ICS, and patients who took classes.

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study 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	241	239	248	
Units: percent				
arithmetic mean (standard deviation)	19.92 (± 23.765)	14 (± 16.733)	33.5 (± 25.593)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of health care resource utilization

End point title	Number of health care resource utilization

End point description:

The analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL and high-dose ICS

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study 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	241	239	248	
Units: proportion of participants				
Hospitalizations	11	14	12	
Emergency department visits	11	12	18	
Unscheduled outpatient visits	72	75	83	
Home visits	3	1	2	
Telephone calls	50	63	58	
Ambulance transports	2	3	5	

Statistical analyses

No statistical analyses for this end point

Secondary: Patient and Clinician assessment of response to treatment

End point title	Patient and Clinician assessment of response to treatment

End point description:

CGIC (clinician 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 a 7-point rating scale, ranging from 1 (Very much Improved), to 7 (Very much Worse). The analysis is based on the primary analysis population, ie, baseline eosinophils >=300/uL and high-dose ICS. Due to the endpoint was implemented after the second protocol amendment, thus not all patients having data to be analyzed.

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study 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	241	239	248	
Units: Count				
CGIC, Improved	109	96	97	
CGIC, Much Improved	82	71	65	
CGIC, Very Much Improved	26	23	14	
CGIC, Total	217	190	176	
PGIC, Improved	109	95	99	
PGIC, Much Improved	83	80	66	
PGIC, Very Much Improved	34	30	17	
PGIC, Total	226	205	182	

Statistical analyses

No statistical analyses for this end point

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

End point title	Annual asthma exacerbation rate in adult and adolescent patients with uncontrolled asthma, 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 analysis population, ie, baseline eosinophils <300/uL and high-dose ICS

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug throguh Study 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	116	125	122	
Units: Rate of event over follow-up time				
least squares mean (confidence interval 95%)	0.78 (0.59 to 1.02)	0.73 (0.55 to 0.95)	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	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.92

Statistical analysis title	Negative binomial analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	negative binomial
Parameter estimate	Rate ratio
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.86

Secondary: Mean change from baseline to Week 56 in Pre-bronchodilator FEV1 (L) value for patient with baseline eosinophils <300/uL

End point title	Mean change from baseline to Week 56 in Pre-bronchodilator FEV1 (L) value for patient with baseline eosinophils <300/uL

End point description:

The analysis is based on the primary analysis population, ie, baseline eosinophils <300/uL and high-dose ICS

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study 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	116	125	122	
Units: Liter				
arithmetic mean (standard deviation)	0.221 (± 0.441)	0.164 (± 0.358)	0.135 (± 0.437)	

Statistical analyses

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.268
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.064
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.049
upper limit	0.176

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.786
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.127
upper limit	0.096

Secondary: Mean change from baseline to Week 56 asthma symptoms score for patient with baseline eosinophils <300/uL

End point title	Mean change from baseline to Week 56 asthma symptoms score for patient with baseline eosinophils <300/uL

End point description:

Asthma symptoms during night time and daytime 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 timepoint 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. The analysis is based on the primary analysis population, ie, baseline eosinophils <300/uL and high-dose ICS.

End point type	Secondary

End point timeframe:

Immediately following the first administration of study drug through Study 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	116	125	122	
Units: Scale of score				
arithmetic mean (standard deviation)	-1.05 (± 1.14)	-0.95 (± 1.13)	-0.88 (± 1.12)	

Statistical analyses

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.287
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	0.13

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.966
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.29

Secondary: Mean change from baseline to Week 56 in ACQ-6 for patients with baseline eosinophils <300/uL

End point title	Mean change from baseline to Week 56 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. The analysis is based on the primary analysis population, ie, baseline eosinophils <300/uL and high-dose ICS

End point type	Secondary

End point timeframe:

Immediately followwing the first administration of study drug through Study 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	116	125	122	
Units: Scale of score				
arithmetic mean (standard deviation)	-1.22 (± 1.16)	-0.98 (± 0.91)	-0.78 (± 0.83)	

Statistical analyses

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.078
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	0.03

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.449
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.16

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

Serious adverse events	Benra 30 mg q.4 weeks	Placebo	Benra 30 mg q.8 weeks
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 438 (10.50%)	61 / 440 (13.86%)	41 / 428 (9.58%)
number of deaths (all causes)	3	1	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer female			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gallbladder cancer			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (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

Gastric cancer			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid adenoma			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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
Uterine leiomyoma			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (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			
Aortic stenosis			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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 / 438 (0.00%)	1 / 440 (0.23%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (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
Phlebitis			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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
Venous thrombosis			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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
General disorders and administration			

site conditions			
Chest pain			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
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 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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 reaction			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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			
Asthma			
subjects affected / exposed	21 / 438 (4.79%)	23 / 440 (5.23%)	19 / 428 (4.44%)
occurrences causally related to treatment / all	0 / 25	0 / 38	1 / 27
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperventilation			

subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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
Nasal polyps			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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
Nasal turbinate hypertrophy			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (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
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (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
Depression			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Anastomotic ulcer			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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

Injury			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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 injury			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
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 complication			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (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
Thermal burn			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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
Toxicity to various agents			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
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 disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			

subjects affected / exposed	1 / 438 (0.23%)	1 / 440 (0.23%)	0 / 428 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
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 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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
Atrial fibrillation			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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 arrest			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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 failure congestive			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (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 disease			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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
Myocardial infarction			

subjects affected / exposed	1 / 438 (0.23%)	1 / 440 (0.23%)	0 / 428 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 438 (0.00%)	2 / 440 (0.45%)	0 / 428 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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			
Cerebrovascular accident			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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
Lumbar radiculopathy			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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
Sciatica			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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
Seizure			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
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 / 438 (0.23%)	0 / 440 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			

subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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
Eye disorders			
Cataract			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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
Gastroduodenitis			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
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	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (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 polyp			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (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
Rectal polyp			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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

Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
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	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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
Cholecystitis chronic			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (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
Cholelithiasis			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (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
Hepatitis alcoholic			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (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
Skin and subcutaneous tissue disorders			
Parakeratosis			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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
Urticaria			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (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
Urticaria papular			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	2 / 438 (0.46%)	0 / 440 (0.00%)	0 / 428 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dupuytren's contracture			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epiphysiolysis			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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 disorder			
subjects affected / exposed	1 / 438 (0.23%)	1 / 440 (0.23%)	0 / 428 (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
Jaw cyst			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (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
Muscular weakness			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (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	1 / 438 (0.23%)	1 / 440 (0.23%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (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
Rotator cuff syndrome			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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
Spinal osteoarthritis			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (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
Spondylolisthesis			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial infection			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (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
Bronchitis			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis haemophilus			

subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (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
Cytomegalovirus hepatitis			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	2 / 428 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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			
subjects affected / exposed	2 / 438 (0.46%)	4 / 440 (0.91%)	0 / 428 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			

subjects affected / exposed	2 / 438 (0.46%)	3 / 440 (0.68%)	0 / 428 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonas bronchitis			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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
Pseudomonas infection			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (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 tract infection bacterial			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (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
Sepsis			
subjects affected / exposed	1 / 438 (0.23%)	0 / 440 (0.00%)	0 / 428 (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
Sinusitis			
subjects affected / exposed	0 / 438 (0.00%)	1 / 440 (0.23%)	0 / 428 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
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			
subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Obesity			

subjects affected / exposed	0 / 438 (0.00%)	0 / 440 (0.00%)	1 / 428 (0.23%)
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	Benra 30 mg q.4 weeks	Placebo	Benra 30 mg q.8 weeks
Total subjects affected by non-serious adverse events			
subjects affected / exposed	244 / 438 (55.71%)	264 / 440 (60.00%)	232 / 428 (54.21%)
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 438 (2.74%)	22 / 440 (5.00%)	18 / 428 (4.21%)
occurrences (all)	12	24	23
Nervous system disorders			
Headache			
subjects affected / exposed	33 / 438 (7.53%)	32 / 440 (7.27%)	34 / 428 (7.94%)
occurrences (all)	63	57	65
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	16 / 438 (3.65%)	6 / 440 (1.36%)	13 / 428 (3.04%)
occurrences (all)	20	6	13
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	50 / 438 (11.42%)	52 / 440 (11.82%)	32 / 428 (7.48%)
occurrences (all)	76	96	50
Cough			
subjects affected / exposed	10 / 438 (2.28%)	8 / 440 (1.82%)	14 / 428 (3.27%)
occurrences (all)	11	12	18
Rhinitis allergic			
subjects affected / exposed	21 / 438 (4.79%)	24 / 440 (5.45%)	16 / 428 (3.74%)
occurrences (all)	25	28	19
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 438 (1.83%)	10 / 440 (2.27%)	14 / 428 (3.27%)
occurrences (all)	10	14	16

Back pain			
subjects affected / exposed	17 / 438 (3.88%)	16 / 440 (3.64%)	11 / 428 (2.57%)
occurrences (all)	18	20	11
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	6 / 438 (1.37%)	14 / 440 (3.18%)	5 / 428 (1.17%)
occurrences (all)	6	19	6
Bronchitis			
subjects affected / exposed	40 / 438 (9.13%)	54 / 440 (12.27%)	45 / 428 (10.51%)
occurrences (all)	51	72	54
Influenza			
subjects affected / exposed	24 / 438 (5.48%)	25 / 440 (5.68%)	12 / 428 (2.80%)
occurrences (all)	27	27	17
Nasopharyngitis			
subjects affected / exposed	90 / 438 (20.55%)	92 / 440 (20.91%)	82 / 428 (19.16%)
occurrences (all)	132	147	131
Pharyngitis			
subjects affected / exposed	17 / 438 (3.88%)	8 / 440 (1.82%)	10 / 428 (2.34%)
occurrences (all)	21	9	10
Rhinitis			
subjects affected / exposed	12 / 438 (2.74%)	17 / 440 (3.86%)	18 / 428 (4.21%)
occurrences (all)	13	22	24
Sinusitis			
subjects affected / exposed	23 / 438 (5.25%)	39 / 440 (8.86%)	21 / 428 (4.91%)
occurrences (all)	31	56	30
Upper respiratory tract infection			
subjects affected / exposed	29 / 438 (6.62%)	42 / 440 (9.55%)	37 / 428 (8.64%)
occurrences (all)	35	53	53

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 May 2014	addition of adolescent patient population, amended incl/exclusion criteria, additional lab measurements
16 March 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