Clinical trial results:
A Phase 2b, Dose-ranging Study to Evaluate the Efficacy and Safety of MEDI-563 in Adults with Uncontrolled Asthma

Summary

EudraCT number	2010-020126-17
Trial protocol	BG
Global end of trial date	15 August 2013

Results information

Result version number	v1
This version publication date	20 February 2016
First version publication date	20 February 2016

Trial information

Trial identification

Sponsor protocol code	MI-CP220

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01238861
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	MedImmune, LLC, an affiliate of AstraZeneca AB
Sponsor organisation address	SE-151 85, Sodertalje, Sweden,
Public contact	Rene van der Merwe, MBChB, MFPM, Medical Officer, MedImmune, LLC, an affiliate of AstraZeneca AB, vandermerwer@medimmune.com
Scientific contact	Rene van der Merwe, MBChB, MFPM, Medical Officer, MedImmune, LLC, an affiliate of AstraZeneca AB, vandermerwer@medimmune.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 August 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the effect of multiple-dose subcutaneous (SC) administration of benralizumab on the annual asthma exacerbation rate (AER) in adult participants with uncontrolled, suspected eosinophilic asthma.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Participating participant signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 December 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	10 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 74
Country: Number of subjects enrolled	Russian Federation: 106
Country: Number of subjects enrolled	Brazil: 62
Country: Number of subjects enrolled	Bulgaria: 96
Country: Number of subjects enrolled	Poland: 61
Country: Number of subjects enrolled	Argentina: 70
Country: Number of subjects enrolled	Peru: 59
Country: Number of subjects enrolled	Mexico: 40
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Colombia: 32
Worldwide total number of subjects	609
EEA total number of subjects	157

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	559
From 65 to 84 years	50
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were stratified based on the protocol defined eosinophilic phenotype (EOS+ versus EOS-) and inhaled corticosteroid (ICS) use during a 3-week screening period. A total of 964 participants were screened out of which 609 were randomized in the study, and of which 606 participants received at least one dose of investigational product.

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, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Eosinophilic phenotype (EOS+) Placebo

Arm description:

EOS+ (defined as ELEN Index [proprietary mathematical algorithm to predict sputum eosinophil's greater than or equal to 2 percent] positive and/or FeNO [fraction of exhaled nitric oxide] greater than or equal to [>=] 50 parts per billion [ppb]) participants received matching placebo subcutaneous injection every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.

Arm type	Placebo
Investigational medicinal product name	Eosinophilic phenotype (EOS+) Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

EOS+ participants received matching placebo injections subcutaneous injection every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.

Arm title	EOS+ Benralizumab, 2 mg

Arm description:

EOS+ participants received benralizumab 2 milligram (mg) subcutaneous injection every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.

Arm type	Experimental
Investigational medicinal product name	Benralizumab
Investigational medicinal product code	MEDI-563
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

EOS+ participants received single benralizumab 2 milligram (mg) injection followed by a single placebo injection subcutaneously.

Arm title	EOS+ Benralizumab, 20 mg

Arm description:

EOS+ participants received benralizumab 20 mg subcutaneous injection every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.

Arm type	Experimental

Investigational medicinal product name	Benralizumab
Investigational medicinal product code	MEDI-563
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

EOS+ participants received single benralizumab 20 mg injection followed by a single placebo injection subcutaneously.

Arm title	EOS+ Benralizumab, 100 mg

Arm description:

EOS+ participants received benralizumab 50 mg as two subcutaneous injections every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.

Arm type	Experimental
Investigational medicinal product name	Benralizumab
Investigational medicinal product code	MEDI-563
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

EOS+ participants received benralizumab 50 mg as two injections subcutaneously every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.

Arm title	Non-eosinophil phenotype (EOS-) Placebo

Arm description:

EOS- (defined as ELEN Index negative and FeNO <50 ppb) participants received matching placebo subcutaneous injections every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.

Arm type	Placebo
Investigational medicinal product name	Non-eosinophil phenotype (EOS-) Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

EOS- (defined as ELEN Index negative and FeNO <50 ppb) participants received matching placebo subcutaneous every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.

Arm title	EOS- Benralizumab, 100 mg

Arm description:

EOS- participants received benralizumab 50 mg as two subcutaneous injections every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.

Arm type	Experimental
Investigational medicinal product name	Benralizumab
Investigational medicinal product code	MEDI-563
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

EOS- participants received benralizumab 50 mg as two injections subcutaneously every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.

Number of subjects in period 1[1]	Eosinophilic phenotype (EOS+) Placebo	EOS+ Benralizumab, 2 mg	EOS+ Benralizumab, 20 mg
Started	80	81	81
Completed	69	73	70
Not completed	11	8	11
Did not meet entry ACQ-6 criteria	-	-	1
Personal problems	-	-	-
Subject moved out of state/area	-	-	1
Lack of compliance	-	-	-
Strongyloides stercoralis antibodies +	-	-	-
Unplanned surgery	1	-	-
Unable to continue visits	-	-	-
Consent withdrawn by subject	6	5	4
Adverse event, non-fatal	-	1	-
Subject traveled to Argentina by 1 year	-	-	1
Incorrect enrollment/randomization	-	-	1
Serious adverse event	-	-	-
Lost to follow-up	4	2	3

Number of subjects in period 1[1]	EOS+ Benralizumab, 100 mg	Non-eosinophil phenotype (EOS-) Placebo	EOS- Benralizumab, 100 mg
Started	82	142	140
Completed	69	129	125
Not completed	13	13	15
Did not meet entry ACQ-6 criteria	-	1	1
Personal problems	1	-	-
Subject moved out of state/area	1	-	-
Lack of compliance	-	-	1
Strongyloides stercoralis antibodies +	1	-	-
Unplanned surgery	-	-	-
Unable to continue visits	1	-	1
Consent withdrawn by subject	8	10	9
Adverse event, non-fatal	-	-	-
Subject traveled to Argentina by 1 year	-	-	-
Incorrect enrollment/randomization	-	1	-
Serious adverse event	-	-	1
Lost to follow-up	1	1	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Not all randomized subjects were treated with study drugs. Hence, the worldwide number enrolled in the trial, which is the same as the number randomized, differs from the number of subjects reported in the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	Eosinophilic phenotype (EOS+) Placebo
Reporting group description:	
EOS+ (defined as ELEN Index [proprietary mathematical algorithm to predict sputum eosinophil's greater than or equal to 2 percent] positive and/or FeNO [fraction of exhaled nitric oxide] greater than or equal to [>=] 50 parts per billion [ppb]) participants received matching placebo subcutaneous injection every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.	
Reporting group title	EOS+ Benralizumab, 2 mg
Reporting group description:	
EOS+ participants received benralizumab 2 milligram (mg) subcutaneous injection every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.	
Reporting group title	EOS+ Benralizumab, 20 mg
Reporting group description:	
EOS+ participants received benralizumab 20 mg subcutaneous injection every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.	
Reporting group title	EOS+ Benralizumab, 100 mg
Reporting group description:	
EOS+ participants received benralizumab 50 mg as two subcutaneous injections every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.	
Reporting group title	Non-eosinophil phenotype (EOS-) Placebo
Reporting group description:	
EOS- (defined as ELEN Index negative and FeNO <50 ppb) participants received matching placebo subcutaneous injections every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.	
Reporting group title	EOS- Benralizumab, 100 mg
Reporting group description:	
EOS- participants received benralizumab 50 mg as two subcutaneous injections every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.	

Reporting group values	Eosinophilic phenotype (EOS+) Placebo	EOS+ Benralizumab, 2 mg	EOS+ Benralizumab, 20 mg
Number of subjects	80	81	81
Age categorical Units: Subjects			
Age Continuous | Units: years			
arithmetic mean	45.6	47.1	46.6
standard deviation	± 11.7	± 12.8	± 13.2
Gender, Male/Female Units: participants			
Female	53	58	48
Male	27	23	33

Reporting group values	EOS+ Benralizumab, 100 mg	Non-eosinophil phenotype (EOS-) Placebo	EOS- Benralizumab, 100 mg
Number of subjects	82	142	140

Age categorical Units: Subjects			

Age Continuous | Units: years			
arithmetic mean	47.8	50	50
standard deviation	± 12.9	± 12.3	± 11.5
Gender, Male/Female Units: participants			
Female	60	100	98
Male	22	42	42

Reporting group values	Total		
Number of subjects	606		
Age categorical Units: Subjects			

Age Continuous | Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: participants			
Female	417		
Male	189		

End points

End points reporting groups

Reporting group title	Eosinophilic phenotype (EOS+) Placebo
Reporting group description:	
EOS+ (defined as ELEN Index [proprietary mathematical algorithm to predict sputum eosinophil's greater than or equal to 2 percent] positive and/or FeNO [fraction of exhaled nitric oxide] greater than or equal to [>=] 50 parts per billion [ppb]) participants received matching placebo subcutaneous injection every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.	
Reporting group title	EOS+ Benralizumab, 2 mg
Reporting group description:	
EOS+ participants received benralizumab 2 milligram (mg) subcutaneous injection every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.	
Reporting group title	EOS+ Benralizumab, 20 mg
Reporting group description:	
EOS+ participants received benralizumab 20 mg subcutaneous injection every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.	
Reporting group title	EOS+ Benralizumab, 100 mg
Reporting group description:	
EOS+ participants received benralizumab 50 mg as two subcutaneous injections every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.	
Reporting group title	Non-eosinophil phenotype (EOS-) Placebo
Reporting group description:	
EOS- (defined as ELEN Index negative and FeNO <50 ppb) participants received matching placebo subcutaneous injections every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.	
Reporting group title	EOS- Benralizumab, 100 mg
Reporting group description:	
EOS- participants received benralizumab 50 mg as two subcutaneous injections every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.	
Subject analysis set title	EOS+ Placebo - Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
EOS+ participants received two placebo injections subcutaneously.	
Subject analysis set title	EOS- Placebo - Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
EOS- participants received two placebo injections subcutaneously.	
Subject analysis set title	EOS- Placebo - mITT Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
EOS- participants received two placebo injections subcutaneously.	
Subject analysis set title	Benralizumab (100 mg) - mITT Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
EOS+ and EOS- participants received two benralizumab 50 mg injections subcutaneously.The modified intent-to-treat (mITT) population included all randomized participants who received any dose of investigational product.	
Subject analysis set title	Placebo - mITT population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Participants received two placebo injections subcutaneously.	
Subject analysis set title	EOS- Benralizumab, 100 mg - Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

EOS- participants received benralizumab 50 mg as two subcutaneous injections every 4 weeks for first 3 doses and then every 8 weeks for next 4 doses up to Week 40.

Subject analysis set title	Benralizumab, 100 mg - PK Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

EOS+ and EOS- participants received two benralizumab 50 mg injections subcutaneously.he Pharmacokinetic (PK) Population included all participants who received at least one dose of benralizumab and had at least one quantifiable PK observation. One participant, randomized to the EOS- placebo group received a single dose of 100 mg benralizumab on Week 16 and was analyzed for PK in the 100 mg benralizumab group.

Primary: Annual Asthma Exacerbation Rate (AER) for Eosinophilic Phenotype (EOS+) Participants

End point title	Annual Asthma Exacerbation Rate (AER) for Eosinophilic Phenotype (EOS+) Participants[1]

End point description:

The annual asthma exacerbation rate (AER) was calculated as the total number of observed exacerbations in each group up to week 52, divided by total duration of person-year follow-up in each group. An asthma exacerbation is defined as a progressive increase of asthma symptoms (cough, wheeze, chest tightness, and/or shortness of breath) that does not resolve after the initiation of rescue medications and remains troublesome for the participant resulting in either 1) use of systemic corticosteroids or increase of a stable systemic maintenance dose for a duration of at least 3 days as prescribed or administered by the investigator or healthcare provider; or 2) participant initiation of systemic corticosteroids for a duration of at least 3 days as outlined in the Asthma Action Plan provided to the participant by the investigator on Day 1. The modified intent-to-treat (mITT) population included all randomized participants who received any dose of investigational product.

End point type	Primary

End point timeframe:

Week 1 up to Week 52

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The EOS- participants were only for exploratory analyses, and hence, data was reported for EOS+ participants in this endpoint.

End point values	Eosinophilic phenotype (EOS+) Placebo	EOS+ Benralizumab, 2 mg	EOS+ Benralizumab, 20 mg	EOS+ Benralizumab, 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	81	81	82
Units: AER events/person-year				
number (not applicable)	0.57	0.65	0.37	0.34

Statistical analyses

Statistical analysis title	Statistical Analysis-1
Comparison groups	Eosinophilic phenotype (EOS+) Placebo v EOS+ Benralizumab, 2 mg

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.781
Method	Poisson Regression Method
Parameter estimate	Rate Ratio
Point estimate	1.09
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.74
upper limit	1.59

Statistical analysis title	Statistical Analysis-3
Comparison groups	Eosinophilic phenotype (EOS+) Placebo v EOS+ Benralizumab, 100 mg
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.096
Method	Poisson Regression Method
Parameter estimate	Rate ratio
Point estimate	0.59
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.4
upper limit	0.89

Statistical analysis title	Statistical Analysis-2
Comparison groups	Eosinophilic phenotype (EOS+) Placebo v EOS+ Benralizumab, 20 mg
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.173
Method	Poisson Regression Method
Parameter estimate	Rate Ratio
Point estimate	0.64
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.42
upper limit	0.97

Secondary: Dose Response in EOS+ Participants

End point title	Dose Response in EOS+ Participants[2]

End point description:

Due to change in planned analysis after unblinding of study data, dose response was not performed.

End point type	Secondary

End point timeframe:

Baseline up to Week 66

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The EOS- participants were only for exploratory analyses, and hence, data was reported for EOS+ participants in this endpoint.

End point values	Eosinophilic phenotype (EOS+) Placebo	EOS+ Benralizumab, 2 mg	EOS+ Benralizumab, 20 mg	EOS+ Benralizumab, 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[3]	0[4]	0[5]	0[6]
Units: participants				

Notes:

[3] - Due to change in planned analysis, dose response was not analyzed.

[4] - Due to change in planned analysis, dose response was not analyzed.

[5] - Due to change in planned analysis, dose response was not analyzed.

[6] - Due to change in planned analysis, dose response was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Serum Trough Concentration for Benralizumab at Steady-State (Ctrough, ss)

End point title	Minimum Observed Serum Trough Concentration for Benralizumab at Steady-State (Ctrough, ss)[7]

End point description:

The Pharmacokinetic (PK) Population included all participants who received at least one dose of benralizumab and had at least one quantifiable PK observation. One participant, randomized to the EOS- placebo group received a single dose of 100 mg benralizumab on Week 16 and was analyzed for PK in the 100 mg benralizumab group.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), Post-dose on Day 1, 6, Week 4, 16, 24, 32, 40, and 52

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The EOS- participants were only for exploratory analyses, and hence, data was reported for EOS+ participants in this endpoint.

End point values	EOS+ Benralizumab, 2 mg	EOS+ Benralizumab, 20 mg	Benralizumab, 100 mg - PK Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	81	81	223	
Units: microgram per milliliter				
arithmetic mean (standard deviation)	34.7 (± 131)	182 (± 180)	869 (± 665)	

Statistical analyses

No statistical analyses for this end point

Secondary: Dose-Normalized Minimum Observed Serum Trough Concentration for Benralizumab at Steady-State (Ctrough, ssD)

End point title	Dose-Normalized Minimum Observed Serum Trough Concentration for Benralizumab at Steady-State (Ctrough, ssD)[8]

End point description:

The PK Population included all participants who received at least one dose of benralizumab and had at least one quantifiable PK observation. One participant, randomized to the EOS- placebo group received a single dose of 100 mg benralizumab on Week 16 and was analyzed for PK in the 100 mg benralizumab group.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), Post-dose on Day 1, 6, Week 4, 16, 24, 32, 40, and 52

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The EOS- participants were only for exploratory analyses, and hence, data was reported for EOS+ participants in this endpoint.

End point values	EOS+ Benralizumab, 2 mg	EOS+ Benralizumab, 20 mg	Benralizumab, 100 mg - PK Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	81	81	223	
Units: microgram per milliliter				
arithmetic mean (standard deviation)	17.3 (± 65.3)	9.1 (± 9.02)	8.69 (± 6.65)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Anti-Drug Antibodies (ADA) to Benralizumab

End point title	Percentage of Participants with Anti-Drug Antibodies (ADA) to Benralizumab[9]

End point description:

Immunogenicity assessment included determination of anti-drug (benralizumab) antibodies in serum samples. ADA positive was defined as a titer >=50 at any point in the study. It was observed at baseline and any visit during the study. The mITT population included all randomized participants who received any dose of investigational product.

End point type	Secondary

End point timeframe:

Baseline up to Week 92

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The EOS- participants were only for exploratory analyses, and hence, data was reported for EOS+ participants in this endpoint.

End point values	EOS+ Benralizumab, 2 mg	EOS+ Benralizumab, 20 mg	EOS+ Benralizumab, 100 mg	EOS+ Placebo - Safety population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	81	81	82	80
Units: percentage of participants				
number (not applicable)	42	30.9	25.6	3.8

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Asthma Control Questionnaire (6-items) (ACQ-6) Score at Week 52

End point title	Change from Baseline in Asthma Control Questionnaire (6-items) (ACQ-6) Score at Week 52[10]

End point description:

Asthma Control Questionnaire (ACQ) is a participant-reported questionnaire to assess the asthma control with 6 items assessing night-time waking, symptoms on waking, activity limitation, shortness of breath, wheeze, and rescue short-acting beta agonist use. Each item was rated on a 7-point Likert scale ranging from 0 (no impairment) to 6 (maximum impairment). Overall ACQ score was the mean of the 6 item scores with a score range of 0 (well controlled) to 6 (extremely poor controlled). Data collected on Day 1 prior to dosing was considered as baseline. Results were reported for overall ACQ score. ACQ-6 score was summarized together for all participants. The mITT population included all randomized participants who received any dose of investigational product. Here "n" signifies participants who were evaluable for this measure for the specified time point for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The EOS- participants were only for exploratory analyses, and hence, data was reported for EOS+ participants in this endpoint.

End point values	Eosinophilic phenotype (EOS+) Placebo	EOS+ Benralizumab, 2 mg	EOS+ Benralizumab, 20 mg	EOS+ Benralizumab, 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	81	81	82
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=80,80,80,82,142,140)	2.7479 (± 0.9762)	2.6479 (± 0.9908)	2.475 (± 0.9106)	2.5346 (± 0.9728)
Change at Week 52 (n=34,42,40,39,64,73)	-0.8922 (± 1.1969)	-1.1032 (± 1.1207)	-1.25 (± 1.2247)	-1.1239 (± 1.2852)

Statistical analyses

Statistical analysis title	Statistical Analysis-1
Comparison groups	Eosinophilic phenotype (EOS+) Placebo v EOS+ Benralizumab, 2 mg
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.125
Method	ANCOVA

Statistical analysis title	Statistical Analysis-3
Comparison groups	Eosinophilic phenotype (EOS+) Placebo v EOS+ Benralizumab, 100 mg
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.057
Method	ANCOVA

Statistical analysis title	Statistical Analysis-2
Comparison groups	Eosinophilic phenotype (EOS+) Placebo v EOS+ Benralizumab, 20 mg
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.074
Method	ANCOVA

Secondary: Change From Baseline in Mean Total Nasal Symptoms Score (TNSS) at Week 52

End point title	Change From Baseline in Mean Total Nasal Symptoms Score (TNSS) at Week 52[11]

End point description:

Total Nasal Symptoms Score (TNSS) is a 3-item questionnaire, the sum of nasal symptoms, namely, nasal obstruction (rhinorrhea), nasal congestion, and nasal itching/sneezing. Each symptom was rated on a scale from 0-3, with 0 representing no symptoms, 1 mild, 2 moderate, and 3 severe symptoms. TNSS score was a summation of the 3 individual nasal symptom. TNSS score could range from 0 to 9 where higher score indicates worsening. Data was summarized by each treatment group. In addition, data was summarized together for "EOS+ and EOS- Placebo" arms and "EOS+ and EOS- benralizumab

100 mg" arms. The mITT population included all randomized participants who received any dose of investigational product. Here "n" signifies participants who were evaluable for this measure for the specified time point for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The EOS- participants were only for exploratory analyses, and hence, data was reported for EOS+ participants in this endpoint.

End point values	EOS+ Benralizumab, 2 mg	EOS+ Benralizumab, 20 mg	Benralizumab (100 mg) - mITT Population	Placebo - mITT population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	81	81	222	222
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=71,27,25,81))	4.8 (± 2)	5.3 (± 1.8)	4.4 (± 2.1)	4.3 (± 2)
Change at Week 52 (n=89,39,39,106)	-0.8 (± 2.01)	-1 (± 2.96)	-0.8 (± 2.24)	-0.4 (± 2.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Mean Asthma Symptom Diary Score at Week 51-52

End point title	Change from baseline in Mean Asthma Symptom Diary Score at Week 51-52[12]

End point description:

Asthma Symptom Diary included 7 questions about the participant symptom and the overall impact of treatment on the disease during the study period. Mean scores of the 7 questions were calculated to identify asthma symptom-free days. Asthma Symptom Diary Scores were analyzed on a bi-weekly basis and compared to baseline scores. Overall symptom score=(daytime frequency score + daytime severity score + nighttime severity score)/3, where total score ranges from 0 to 9. Higher score represents worsening. Mean asthma symptom diary score were summarized together for all participants. Data was summarized by each treatment group. In addition, data was summarized together for "EOS+ and EOS- Placebo" arms and "EOS+ and EOS- benralizumab 100 mg" arms. The mITT population included all randomized participants who received any dose of investigational product. Here "n" signifies participants who were evaluable for this measure for the specified time point for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline up to Week 51-52

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The EOS- participants were only for exploratory analyses, and hence, data was reported for EOS+ participants in this endpoint.

End point values	EOS+ Benralizumab, 2 mg	EOS+ Benralizumab, 20 mg	Benralizumab (100 mg) - mITT Population	Placebo - mITT population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	81	81	222	222
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=204,72,74,210)	1.65 (± 0.65)	1.6 (± 0.61)	1.6 (± 0.62)	1.58 (± 0.6)
Change at Week 51-52 (n=111,36,39,111)	-0.56 (± 0.76)	-0.56 (± 0.69)	-0.53 (± 0.67)	-0.37 (± 0.61)

Statistical analyses

Statistical analysis title	Statistical Analysis-1
Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	606
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.131
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.182
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.336
upper limit	-0.028

Statistical analysis title	Statistical Analysis-3
Comparison groups	Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.097
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.247
upper limit	-0.032

Statistical analysis title	Statistical Analysis-2
Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	606
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.126
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.173
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.317
upper limit	-0.028

Secondary: Change from Baseline in Rescue Medication Use at Week 51-52

End point title	Change from Baseline in Rescue Medication Use at Week 51-

End point description:

Participants were provided inhalers of the same dose (medium- or high-dose) inhaled corticosteroid (ICS) plus long-acting beta antagonist (LABA) combination product as baseline prophylactic medication and continued with same dose throughout the study. Rescue medications such as short-term beta2 agonists were used as first-line treatment for worsening asthma symptoms. Investigator prescribed additional short term asthma controller medications included additional ICS, theophylline, inhaled cromones or antimuscarinics; if asthma symptoms remained mild but not resolved. If asthma symptoms worsened, received an oral corticosteroid burst. All rescue medications use with prophylactic medication (+ prophylactic) and without prophylactic medication (- prophylactic) was recorded in asthma symptom dairy and analyzed on a bi-weekly basis and compared to baseline scores. Here "n" signifies participants who were evaluable for this measure for the specified time point for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline up to Week 51-52

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The EOS- participants were only for exploratory analyses, and hence, data was reported for EOS+ participants in this endpoint.

End point values	EOS+ Benralizumab, 2 mg	EOS+ Benralizumab, 20 mg	Benralizumab (100 mg) - mITT Population	Placebo - mITT population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	81[14]	81[15]	222[16]	222[17]
Units: rescue medication per 2 weeks				
arithmetic mean (standard deviation)				
Baseline without prophylactic (n=204,72,74,210)	3.57 (± 3.67)	3.82 (± 4.34)	3.16 (± 2.82)	3.09 (± 2.55)

Baseline with prophylactic (n=204,72,74,210)	4.71 (± 5.56)	5.24 (± 6.4)	4.22 (± 3.9)	4.07 (± 3.34)
Change Week 51-52 - prophylactic(n=111,36,39,111)	-1.4116 (± 2.8722)	-1.8804 (± 5.3129)	-1.1589 (± 2.0086)	-1.254 (± 2.4571)
Change Week 51-52 +prophylactic(n=111,36,39,111)	-1.681 (± 4.2247)	-2.5118 (± 7.6814)	-1.4693 (± 2.5603)	-1.6855 (± 3.2875)

Notes:

[14] - mITT population

[15] - mITT population

[16] - mITT population

[17] - mITT population

Statistical analyses

Statistical analysis title	Statistical Analysis-1
Statistical analysis description:	
Analysis reported for rescue medication use without prophylactic at Week 51-52.	
Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	606
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.642
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.174
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.654
upper limit	0.306

Statistical analysis title	Statistical Analysis-2
Statistical analysis description:	
Analysis reported for rescue medication use without prophylactic at Week 51-52.	
Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	606
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.824
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.111
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.533
upper limit	0.756

Statistical analysis title	Statistical Analysis-3
Statistical analysis description:	
Analysis reported for rescue medication use without prophylactic at Week 51-52.	
Comparison groups	Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.91
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.029
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.297
upper limit	0.355

Statistical analysis title	Statistical Analysis-4
Statistical analysis description:	
Analysis reported for rescue medication use with prophylactic at Week 51-52.	
Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	606
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.992
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.004
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.602
upper limit	0.593

Statistical analysis title	Statistical Analysis-5
Statistical analysis description:	
Analysis reported for rescue medication use with prophylactic at Week 51-52.	
Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v Placebo - mITT population v Benralizumab (100 mg) - mITT Population

Number of subjects included in analysis	606
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.624
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.337
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.548
upper limit	1.222

Statistical analysis title	Statistical Analysis-6
Statistical analysis description:	
Analysis reported for rescue medication use with prophylactic at Week 51-52.	
Comparison groups	Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.645
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.15
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.267
upper limit	0.567

Secondary: Change From Baseline in Forced Expiratory Volume in 1 Second (FEV1) at Week 52

End point title	Change From Baseline in Forced Expiratory Volume in 1 Second (FEV1) at Week 52[18]

End point description:

FEV1 was the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration. Data was summarized by each treatment group. In addition, data was summarized together for "EOS+ and EOS- Placebo" arms and "EOS+ and EOS- benralizumab 100 mg" arms. The mITT population included all randomized participants who received any dose of investigational product. Here "n" signifies participants who were evaluable for this measure for the specified time point for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline and Week 52

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The EOS- participants were only for exploratory analyses, and hence, data was reported for EOS+ participants in this endpoint.

End point values	EOS+ Benralizumab, 2 mg	EOS+ Benralizumab, 20 mg	Benralizumab (100 mg) - mITT Population	Placebo - mITT population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	81	81	222	222
Units: liters				
arithmetic mean (standard deviation)				
Baseline (n=215,80,81,218)	1.978 (± 0.701)	2.08 (± 0.751)	2.012 (± 0.672)	2.033 (± 0.669)
Change at Week 52 (n=150,51,58,160)	0.1631 (± 0.4691)	0.1847 (± 0.5234)	0.0998 (± 0.3541)	0.0098 (± 0.3615)

Statistical analyses

Statistical analysis title	Statistical Analysis-1
Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	606
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.014
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.157
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.076
upper limit	0.237

Statistical analysis title	Statistical Analysis-2
Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	606
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.004
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.184

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.102
upper limit	0.266

Statistical analysis title	Statistical Analysis-3
Comparison groups	Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.026
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.091
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.039
upper limit	0.143

Secondary: Change From Baseline in Mean Forced Vital Capacity (FVC) at Week 52

End point title	Change From Baseline in Mean Forced Vital Capacity (FVC) at Week 52[19]

End point description:

Forced Vital Capacity (FVC) was the volume of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. The mITT population included all randomized participants who received any dose of investigational product. Here "n" signifies participants who were evaluable for this measure for the specified time point for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline and Week 52

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The EOS- participants were only for exploratory analyses, and hence, data was reported for EOS+ participants in this endpoint.

End point values	EOS+ Benralizumab, 2 mg	EOS+ Benralizumab, 20 mg	EOS+ Benralizumab, 100 mg	EOS+ Placebo - Safety population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	81	81	82	80
Units: liters				
arithmetic mean (standard deviation)				
Baseline (n=80,80,81,82,135,136)	3.069 (± 0.957)	3.285 (± 1.028)	3.11 (± 0.851)	3.282 (± 1.03)

Change at Week 52 (n=51,51,58,59,99,101)	0.129 (± 0.565)	0.19 (± 0.586)	0.166 (± 0.445)	0.029 (± 0.514)

Statistical analyses

Statistical analysis title	Statistical Analysis-1
Comparison groups	EOS+ Benralizumab, 20 mg v EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 100 mg v EOS+ Placebo - Safety population
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.384
Method	ANCOVA

Statistical analysis title	Statistical Analysis-3
Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v EOS+ Benralizumab, 100 mg v EOS+ Placebo - Safety population
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.134
Method	ANCOVA

Statistical analysis title	Statistical Analysis-2
Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v EOS+ Benralizumab, 100 mg v EOS+ Placebo - Safety population
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.092
Method	ANCOVA

Secondary: Change From Baseline in Peak Expiratory Flow (PEF) at Week 52	
End point title	Change From Baseline in Peak Expiratory Flow (PEF) at Week 52[20]

End point description:

The PEF is a participant’s maximum speed of expiration, as measured with a peak flow meter. Peak flow testing for PEF was performed while sitting or standing prior to using any medication (if needed) for asthma. Home PEF was summarized separately for morning and evening assessments. Data was summarized by each treatment group. In addition, data was summarized together for "EOS+ and EOS-

Placebo” arms and “EOS+ and EOS- benralizumab 100 mg” arms. The mITT population included all randomized participants who received any dose of investigational product. Here "n" signifies participants who were evaluable for this measure for the specified time point for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline and Week 52

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The EOS- participants were only for exploratory analyses, and hence, data was reported for EOS+ participants in this endpoint.

End point values	EOS+ Benralizumab, 2 mg	EOS+ Benralizumab, 20 mg	Benralizumab (100 mg) - mITT Population	Placebo - mITT population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	81	81	222	222
Units: liters per minute				
arithmetic mean (standard deviation)				
Baseline (n=215,80,81,218)	325.5 (± 101.6)	323.1 (± 100.8)	323.8 (± 101.7)	319.3 (± 104.7)
Change at Week 52 (n=150,51,58,160)	29 (± 64.1)	45.9 (± 95.5)	26.6 (± 66.3)	13 (± 64.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Asthma Quality of Life Questionnaire (Standardized Version) (AQLQ[S]) Score at Week 52

End point title	Change From Baseline in Asthma Quality of Life Questionnaire (Standardized Version) (AQLQ[S]) Score at Week 52[21]

End point description:

AQLQ: a 32-item questionnaire evaluating quality of life of participants with asthma including 4 domains (symptoms, activity limitations, emotional function, and environmental stimuli). Participants were asked to recall their experiences during the previous 2 weeks and to score each of the 32 questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment) and mean response was calculated as overall score. The 4 domain scores were the means of the responses to the questions in each of the domains. Overall AQLQ score and 4 domain scores ranged from 7 (no impairment) to 1 (severe impairment). The AQLQ(S) responses were categorized as improvement (defined as change from baseline >=0.5), no change (defined as change from baseline >= -0.5 to < 0.5), and worse (defined as change from baseline < -0.5). Here "n" signifies participants who were evaluable for this measure for the specified time point for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline and Week 52

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The EOS- participants were only for exploratory analyses, and hence, data was reported for EOS+ participants in this endpoint.

End point values	EOS+ Benralizumab, 2 mg	EOS+ Benralizumab, 20 mg	Benralizumab (100 mg) - mITT Population	Placebo - mITT population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	81[22]	81[23]	222[24]	222[25]
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=214,78,80,217)	3.72 (± 1.17)	3.79 (± 1.06)	3.72 (± 1.01)	3.72 (± 1.04)
Change at Week 52 (n=88,39,38,105)	1.2612 (± 1.2082)	1.4474 (± 1.4262)	1.1223 (± 1.2636)	0.9634 (± 1.3342)

Notes:

[22] - mITT population

[23] - mITT population

[24] - mITT population

[25] - mITT population

Statistical analyses

Statistical analysis title	Statistical Analysis-1
Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	606
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.069
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.404
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.121
upper limit	0.687

Statistical analysis title	Statistical Analysis-2
Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	606
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.049
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.462
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.163
upper limit	0.761

Statistical analysis title	Statistical Analysis-3
Comparison groups	Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.168
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.238
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.017
upper limit	0.459

Secondary: Change From Baseline in European Quality of Life - 5 Dimensions (EQ-5D) Health State Evaluation at Week 52

End point title	Change From Baseline in European Quality of Life - 5 Dimensions (EQ-5D) Health State Evaluation at Week 52[26]

End point description:

The utility-based EQ-5D questionnaire comprises of two parts and provides a generic measure of health for clinical and economic appraisal. The health state valuation was the summary score of mobility, self-care, usual activities, pain/discomfort and anxiety/depression on a 3 category scale (no problem, moderate problem, severe problems). Score is transformed and results in a total score range -0.594 to 1.000; higher score indicates a better health state. Data was summarized by each treatment group. In addition, data was summarized together for "EOS+ and EOS- Placebo" arms and "EOS+ and EOS- benralizumab 100 mg" arms. The mITT population included all randomized participants who received any dose of investigational product. Here "n" signifies participants who were evaluable for this measure for the specified time point for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline and Week 52

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The EOS- participants were only for exploratory analyses, and hence, data was reported for EOS+ participants in this endpoint.

End point values	EOS+ Benralizumab, 2 mg	EOS+ Benralizumab, 20 mg	Benralizumab (100 mg) - mITT Population	Placebo - mITT population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	81	81	222	222
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=213,79,74,209)	0.7418 (± 0.2376)	0.7877 (± 0.1878)	0.7679 (± 0.1623)	0.7629 (± 0.2153)

Change at Week 52 (n=148,58,53,161)	0.0822 (± 0.3137)	0.1223 (± 0.2132)	0.0824 (± 0.2179)	0.0853 (± 0.2096)

Statistical analyses

Statistical analysis title	Statistical Analysis-1
Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	606
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.51
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.058
upper limit	0.019

Statistical analysis title	Statistical Analysis-3
Comparison groups	Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.599
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.011
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.016
upper limit	0.038

Statistical analysis title	Statistical Analysis-2
Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v Placebo - mITT population v Benralizumab (100 mg) - mITT Population

Number of subjects included in analysis	606
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.113
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.041
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.008
upper limit	0.074

Secondary: Change From Baseline in EQ-5D Visual Analog Scale (VAS) at Week 52

End point title	Change From Baseline in EQ-5D Visual Analog Scale (VAS) at Week 52[27]

End point description:

The utility-based EQ-5D questionnaire comprises of two parts and provides a generic measure of health for clinical and economic appraisal. The EQ-5D VAS was measured from 0 (worst imaginable health state) to 100 (best imaginable health state). Data was summarized by each treatment group. In addition, data was summarized together for "EOS+ and EOS- Placebo" arms and "EOS+ and EOS- benralizumab 100 mg" arms. The mITT population included all randomized participants who received any dose of investigational product. Here "n" signifies participants who were evaluable for this measure for the specified time point for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline and Week 52

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The EOS- participants were only for exploratory analyses, and hence, data was reported for EOS+ participants in this endpoint.

End point values	EOS+ Benralizumab, 2 mg	EOS+ Benralizumab, 20 mg	Benralizumab (100 mg) - mITT Population	Placebo - mITT population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	81	81	222	222
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=213,79,74,208)	65.4937 (± 18.5063)	64.3378 (± 18.1427)	64.625 (± 19.7778)	65.0798 (± 17.8903)
Change at Week 52 (n=148,58,53,161)	12.5517 (± 20.8008)	15.4906 (± 21.7297)	13.7391 (± 20.5139)	12.8041 (± 19.1036)

Statistical analyses

Statistical analysis title	Statistical Analysis-1
Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v Placebo - mITT population v Benralizumab (100 mg) - mITT

	Population
Number of subjects included in analysis	606
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.871
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.373
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-3.333
upper limit	2.586

Statistical analysis title	Statistical Analysis-3
Comparison groups	Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.503
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.139
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.041
upper limit	3.319

Statistical analysis title	Statistical Analysis-2
Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	606
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.227
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.857
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.175
upper limit	5.889

Secondary: Change From Baseline in Percentage of Nocturnal Awakening-Free Nights at Week 51-52

End point title	Change From Baseline in Percentage of Nocturnal Awakening-Free Nights at Week 51-52[28]

End point description:

Percentage of nocturnal awakening-free nights were analyzed on a bi-weekly basis and compared to baseline scores. Data was summarized by each treatment group. In addition, data was summarized together for "EOS+ and EOS- Placebo" arms and "EOS+ and EOS- benralizumab 100 mg" arms.

End point type	Secondary

End point timeframe:

Baseline up to Week 51-52

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The EOS- participants were only for exploratory analyses, and hence, data was reported for EOS+ participants in this endpoint.

End point values	EOS+ Benralizumab, 2 mg	EOS+ Benralizumab, 20 mg	Benralizumab (100 mg) - mITT Population	Placebo - mITT population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	81	81	222	222
Units: percent nocturnal awakening-free nights				
arithmetic mean (standard deviation)				
Baseline (n=204,72,74,210)	45.07 (± 40.04)	51.57 (± 39.72)	50.92 (± 37.72)	52.05 (± 36.96)
Change at Week 51-52 (n=111,36,39,111)	27.1749 (± 41.7342)	29.6181 (± 38.4315)	23.3054 (± 36.2761)	19.7595 (± 39.1388)

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Placebo, EOS+ Benralizumab, 2 mg

Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	606
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.55 [29]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.907

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-4.483
upper limit	12.297

Notes:

[29] - P-value was calculated by ANCOVA with treatment, baseline inhaled steroid status and baseline observed value as covariates.

Statistical analysis title	Statistical analysis 3
Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	606
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.413 [30]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.54
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-2.006
upper limit	9.086

Notes:

[30] - P-value was calculated by ANCOVA with treatment, baseline inhaled steroid status and baseline observed value as covariates.

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
Placebo, EOS+ Benralizumab, 20 mg	
Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	606
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.215 [31]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	7.659
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.262
upper limit	15.579

Notes:

[31] - P-value was calculated by ANCOVA with treatment, baseline inhaled steroid status and baseline observed value as covariates.

Secondary: Change From Baseline in Mean Fraction Exhaled Nitric Oxide (FeNO) at Week 52

End point title	Change From Baseline in Mean Fraction Exhaled Nitric Oxide

	(FeNO) at Week 52[32]

End point description:

Data was summarized by each treatment group. In addition, data was summarized together for "EOS+ and EOS- Placebo" arms and "EOS+ and EOS- benralizumab 100 mg" arms.

End point type	Secondary

End point timeframe:

Baseline and Week 52

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The EOS- participants were only for exploratory analyses, and hence, data was reported for EOS+ participants in this endpoint.

End point values	EOS+ Benralizumab, 2 mg	EOS+ Benralizumab, 20 mg	Benralizumab (100 mg) - mITT Population	Placebo - mITT population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	81	81	222	222
Units: parts per billion				
arithmetic mean (standard deviation)				
Baseline (n=222,81,81,222)	39.52 (± 32.67)	40.79 (± 31.03)	26.68 (± 23.1)	26.88 (± 23.57)
Change at Week 52 (n=148,57,56,157)	-3.2222 (± 33.2543)	-6.1905 (± 30.1103)	1.4384 (± 28.909)	1.2523 (± 16.02)

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Placebo, EOS+ Benralizumab, 2 mg

Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	606
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.896 [33]
Method	ANCOVA

Notes:

[33] - P-value was calculated by ANCOVA with treatment, baseline inhaled steroid status and baseline observed value as covariates.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Placebo, EOS+ Benralizumab, 20 mg

Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v Placebo - mITT population v Benralizumab (100 mg) - mITT Population

Number of subjects included in analysis	606
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.944 [34]
Method	ANCOVA

Notes:

[34] - P-value was calculated by ANCOVA with treatment, baseline inhaled steroid status and baseline observed value as covariates.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Placebo, Benralizumab (100 mg)

Comparison groups	EOS+ Benralizumab, 2 mg v EOS+ Benralizumab, 20 mg v Placebo - mITT population v Benralizumab (100 mg) - mITT Population
Number of subjects included in analysis	606
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.667 [35]
Method	ANCOVA

Notes:

[35] - P-value was calculated by ANCOVA with treatment, baseline inhaled steroid status and baseline observed value as covariates.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From initiation of investigational product administration up to Week 92

Adverse event reporting additional description:

The safety population included all participants who received any investigational product and had safety data available for analysis. One participant, randomized to the EOS- placebo group received a single dose of 100 mg benralizumab on Week 16 and was analyzed for safety in the 100 mg benralizumab group .

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	EOS POS Placebo

Reporting group description:

EOS+ participants received two placebo injections subcutaneously.

Reporting group title	EOS POS Benralizumab 2 mg

Reporting group description:

EOS+ participants received single benralizumab 2 milligram (mg) injection followed by a single placebo injection subcutaneously.

Reporting group title	EOS POS Benralizumab 20 mg

Reporting group description:

EOS+ participants received single benralizumab 20 mg injection followed by a single placebo injection subcutaneously.

Reporting group title	EOS POS Benralizumab 100 mg

Reporting group description:

EOS+ participants received two benralizumab 50 mg injections subcutaneously.

Reporting group title	EOS NEG Placebo

Reporting group description:

EOS- participants received two placebo injections subcutaneously.

Reporting group title	EOS NEG Benralizumab 100 mg

Reporting group description:

EOS- participants received two benralizumab 50 mg injections subcutaneously.

Serious adverse events	EOS POS Placebo	EOS POS Benralizumab 2 mg	EOS POS Benralizumab 20 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 80 (8.75%)	10 / 81 (12.35%)	6 / 81 (7.41%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibrous histiocytoma			

subjects affected / exposed	1 / 80 (1.25%)	0 / 81 (0.00%)	0 / 81 (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
Malignant melanoma			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid neoplasm			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyarteritis nodosa			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic reaction			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Asthma			
subjects affected / exposed	2 / 80 (2.50%)	2 / 81 (2.47%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthmatic crisis			
subjects affected / exposed	1 / 80 (1.25%)	0 / 81 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal polyps			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung diseas			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Insomnia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Abdominal wound dehiscen			

subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	0 / 80 (0.00%)	1 / 81 (1.23%)	0 / 81 (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 infarct			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	2 / 81 (2.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachyca			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 80 (0.00%)	1 / 81 (1.23%)	0 / 81 (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
Grand mal convulsion			

subjects affected / exposed	0 / 80 (0.00%)	1 / 81 (1.23%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 80 (1.25%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 80 (1.25%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 80 (1.25%)	0 / 81 (0.00%)	0 / 81 (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
Gastrooesophageal reflux			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	1 / 80 (1.25%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Cholecystitis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erythema nodosum			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eczema			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 80 (0.00%)	2 / 81 (2.47%)	0 / 81 (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
Musculoskeletal pain			
subjects affected / exposed	0 / 80 (0.00%)	1 / 81 (1.23%)	0 / 81 (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
Osteochondrosis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 81 (1.23%)	0 / 81 (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	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eczema infected			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis infectious			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis viral			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 81 (1.23%)	0 / 81 (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 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural cellulit			
subjects affected / exposed	0 / 80 (0.00%)	1 / 81 (1.23%)	0 / 81 (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
Postoperative wound infe			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis bacterial			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 81 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	EOS POS Benralizumab 100 mg	EOS NEG Placebo	EOS NEG Benralizumab 100 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 82 (7.32%)	16 / 141 (11.35%)	18 / 141 (12.77%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibrous histiocytoma			

subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid neoplasm			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	1 / 82 (1.22%)	0 / 141 (0.00%)	0 / 141 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 82 (1.22%)	0 / 141 (0.00%)	0 / 141 (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
Polyarteritis nodosa			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 82 (1.22%)	0 / 141 (0.00%)	0 / 141 (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
Anaphylactic reaction			
subjects affected / exposed	0 / 82 (0.00%)	1 / 141 (0.71%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Asthma			
subjects affected / exposed	2 / 82 (2.44%)	8 / 141 (5.67%)	5 / 141 (3.55%)
occurrences causally related to treatment / all	0 / 3	0 / 14	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthmatic crisis			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal polyps			
subjects affected / exposed	1 / 82 (1.22%)	0 / 141 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 82 (0.00%)	1 / 141 (0.71%)	0 / 141 (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
Interstitial lung diseas			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 82 (0.00%)	1 / 141 (0.71%)	0 / 141 (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
Insomnia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 141 (0.71%)	0 / 141 (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, poisoning and procedural complications			
Abdominal wound dehiscen			

subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarct			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 82 (0.00%)	1 / 141 (0.71%)	0 / 141 (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 acute			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachyca			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Grand mal convulsion			

subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	1 / 141 (0.71%)
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	0 / 82 (0.00%)	0 / 141 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 82 (1.22%)	0 / 141 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux			
subjects affected / exposed	0 / 82 (0.00%)	1 / 141 (0.71%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 82 (0.00%)	1 / 141 (0.71%)	0 / 141 (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
Umbilical hernia			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Cholecystitis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 141 (0.71%)	0 / 141 (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 acute			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erythema nodosum			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eczema			
subjects affected / exposed	0 / 82 (0.00%)	1 / 141 (0.71%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondrosis			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Spinal osteoarthritis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 141 (0.71%)	0 / 141 (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			
Bronchitis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 141 (0.71%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eczema infected			
subjects affected / exposed	0 / 82 (0.00%)	1 / 141 (0.71%)	0 / 141 (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
Enteritis infectious			
subjects affected / exposed	0 / 82 (0.00%)	1 / 141 (0.71%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis viral			
subjects affected / exposed	1 / 82 (1.22%)	0 / 141 (0.00%)	0 / 141 (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
Herpes zoster			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 82 (1.22%)	1 / 141 (0.71%)	3 / 141 (2.13%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract			
subjects affected / exposed	0 / 82 (0.00%)	1 / 141 (0.71%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural cellulit			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infe			
subjects affected / exposed	1 / 82 (1.22%)	0 / 141 (0.00%)	0 / 141 (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
Tonsillitis bacterial			
subjects affected / exposed	1 / 82 (1.22%)	0 / 141 (0.00%)	0 / 141 (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			
Hypercholesterolaemia			
subjects affected / exposed	0 / 82 (0.00%)	0 / 141 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	EOS POS Placebo	EOS POS Benralizumab 2 mg	EOS POS Benralizumab 20 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 80 (55.00%)	54 / 81 (66.67%)	57 / 81 (70.37%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 80 (1.25%)	3 / 81 (3.70%)	0 / 81 (0.00%)
occurrences (all)	2	3	0

Nervous system disorders			
Headache			
subjects affected / exposed	8 / 80 (10.00%)	8 / 81 (9.88%)	6 / 81 (7.41%)
occurrences (all)	13	13	10
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 80 (0.00%)	2 / 81 (2.47%)	2 / 81 (2.47%)
occurrences (all)	0	2	4
Injection site pain			
subjects affected / exposed	0 / 80 (0.00%)	6 / 81 (7.41%)	4 / 81 (4.94%)
occurrences (all)	0	6	17
Pyrexia			
subjects affected / exposed	1 / 80 (1.25%)	4 / 81 (4.94%)	3 / 81 (3.70%)
occurrences (all)	1	4	3
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 80 (2.50%)	3 / 81 (3.70%)	2 / 81 (2.47%)
occurrences (all)	3	3	2
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	30 / 80 (37.50%)	28 / 81 (34.57%)	24 / 81 (29.63%)
occurrences (all)	51	59	42
Rhinitis allergic			
subjects affected / exposed	3 / 80 (3.75%)	3 / 81 (3.70%)	8 / 81 (9.88%)
occurrences (all)	3	5	13
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 80 (1.25%)	4 / 81 (4.94%)	5 / 81 (6.17%)
occurrences (all)	1	5	6
Back pain			
subjects affected / exposed	3 / 80 (3.75%)	4 / 81 (4.94%)	2 / 81 (2.47%)
occurrences (all)	3	4	2
Myalgia			
subjects affected / exposed	1 / 80 (1.25%)	2 / 81 (2.47%)	3 / 81 (3.70%)
occurrences (all)	1	2	3
Infections and infestations			

Influenza			
subjects affected / exposed	4 / 80 (5.00%)	3 / 81 (3.70%)	7 / 81 (8.64%)
occurrences (all)	4	5	7
Sinusitis			
subjects affected / exposed	3 / 80 (3.75%)	4 / 81 (4.94%)	3 / 81 (3.70%)
occurrences (all)	6	7	3
Acute sinusitis			
subjects affected / exposed	3 / 80 (3.75%)	4 / 81 (4.94%)	2 / 81 (2.47%)
occurrences (all)	7	6	2
Bronchitis			
subjects affected / exposed	3 / 80 (3.75%)	8 / 81 (9.88%)	6 / 81 (7.41%)
occurrences (all)	4	10	8
Nasopharyngitis			
subjects affected / exposed	8 / 80 (10.00%)	11 / 81 (13.58%)	7 / 81 (8.64%)
occurrences (all)	13	19	13
Pharyngitis			
subjects affected / exposed	3 / 80 (3.75%)	8 / 81 (9.88%)	3 / 81 (3.70%)
occurrences (all)	3	10	3
Rhinitis			
subjects affected / exposed	3 / 80 (3.75%)	3 / 81 (3.70%)	3 / 81 (3.70%)
occurrences (all)	3	3	3
Upper respiratory tract			
subjects affected / exposed	4 / 80 (5.00%)	7 / 81 (8.64%)	7 / 81 (8.64%)
occurrences (all)	6	12	8
Urinary tract infection			
subjects affected / exposed	4 / 80 (5.00%)	2 / 81 (2.47%)	1 / 81 (1.23%)
occurrences (all)	4	3	1

Non-serious adverse events	EOS POS Benralizumab 100 mg	EOS NEG Placebo	EOS NEG Benralizumab 100 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 82 (82.93%)	94 / 141 (66.67%)	93 / 141 (65.96%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 82 (3.66%)	4 / 141 (2.84%)	10 / 141 (7.09%)
occurrences (all)	3	4	12
Nervous system disorders			

Headache			
subjects affected / exposed	9 / 82 (10.98%)	8 / 141 (5.67%)	13 / 141 (9.22%)
occurrences (all)	10	9	17
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	8 / 82 (9.76%)	0 / 141 (0.00%)	10 / 141 (7.09%)
occurrences (all)	17	0	17
Injection site pain			
subjects affected / exposed	2 / 82 (2.44%)	6 / 141 (4.26%)	2 / 141 (1.42%)
occurrences (all)	3	12	4
Pyrexia			
subjects affected / exposed	1 / 82 (1.22%)	1 / 141 (0.71%)	2 / 141 (1.42%)
occurrences (all)	1	1	2
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 82 (1.22%)	2 / 141 (1.42%)	2 / 141 (1.42%)
occurrences (all)	1	2	2
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	26 / 82 (31.71%)	42 / 141 (29.79%)	42 / 141 (29.79%)
occurrences (all)	36	67	77
Rhinitis allergic			
subjects affected / exposed	6 / 82 (7.32%)	4 / 141 (2.84%)	5 / 141 (3.55%)
occurrences (all)	8	8	11
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 82 (3.66%)	1 / 141 (0.71%)	3 / 141 (2.13%)
occurrences (all)	3	1	3
Back pain			
subjects affected / exposed	2 / 82 (2.44%)	1 / 141 (0.71%)	3 / 141 (2.13%)
occurrences (all)	4	1	3
Myalgia			
subjects affected / exposed	2 / 82 (2.44%)	1 / 141 (0.71%)	5 / 141 (3.55%)
occurrences (all)	3	1	5
Infections and infestations			

Influenza			
subjects affected / exposed	6 / 82 (7.32%)	10 / 141 (7.09%)	6 / 141 (4.26%)
occurrences (all)	6	11	6
Sinusitis			
subjects affected / exposed	2 / 82 (2.44%)	2 / 141 (1.42%)	0 / 141 (0.00%)
occurrences (all)	3	2	0
Acute sinusitis			
subjects affected / exposed	3 / 82 (3.66%)	2 / 141 (1.42%)	6 / 141 (4.26%)
occurrences (all)	3	4	8
Bronchitis			
subjects affected / exposed	3 / 82 (3.66%)	13 / 141 (9.22%)	9 / 141 (6.38%)
occurrences (all)	4	20	11
Nasopharyngitis			
subjects affected / exposed	13 / 82 (15.85%)	5 / 141 (3.55%)	13 / 141 (9.22%)
occurrences (all)	16	6	17
Pharyngitis			
subjects affected / exposed	7 / 82 (8.54%)	5 / 141 (3.55%)	6 / 141 (4.26%)
occurrences (all)	9	5	6
Rhinitis			
subjects affected / exposed	2 / 82 (2.44%)	5 / 141 (3.55%)	3 / 141 (2.13%)
occurrences (all)	3	5	7
Upper respiratory tract			
subjects affected / exposed	5 / 82 (6.10%)	10 / 141 (7.09%)	11 / 141 (7.80%)
occurrences (all)	6	12	14
Urinary tract infection			
subjects affected / exposed	3 / 82 (3.66%)	5 / 141 (3.55%)	3 / 141 (2.13%)
occurrences (all)	4	5	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 April 2011	The exclusion criteria for mitigation of parasitic infection associated with eosinophil depletion due to benralizumab were modified. Added an exploratory objective to analyse the performance of different helminth serology assays. Exclusion criterion 1 was revised to exclude subjects with allergic bronchopulmonary aspergillosis from participation. Exclusion criterion 27 was revised to ensure subjects were able to perform spirometry during the study. Exclusion criterion 28 was added to exclude subjects who used any oral or ophthalmic β-adrenergic antagonist. Withdrawal criterion was added that a subject would be discontinued from further investigational product administration based on an AE as determined by the sponsor. Withdrawal criterion added that the development of S stercoralis in subjects with chronic OCS-dependent asthma. Schedule of study procedures: The hepatitis A antibody test was removed from screening. Added that unblinded staff must not administer investigational product to the subject to maintain the integrity of the study blind. Added Asthma Symptom Diary Anchoring Questions. Schedule of study procedures: Hepatitis A antibody test was removed from screening. Schedule of study procedures: An early discontinuation visit was added and added serology testing for S stercoralis in subjects with chronic oral corticosteroiddependent asthma at Weeks 16, 32, 52, and 66. Added 4-day window to Screening Visit. Added collection of time of administration of the first injection of investigational product. Added Early Discontinuation Visit for subjects who discontinued the study prematurely. Added footnote under list of serum chemistries to conduct and assess tests for AST, ALT, ALP, and total bilirubin concurrently. Added procedures for parasite serology testing of S stercoralis, and for collection and analysis of stool samples. Added section on hepatic function abnormality as a measure of safety. Changed interim analysis to primary analysis.
14 November 2011	Changed total number of subjects to be randomized to 522 and total number of EOS+ subjects to be randomized to 280; changed number of EOS+ subjects in each treatment regimen from 60 to 70. Changed number of months for expected enrollment to 15-18. Changed number of weeks that subjects should return to the study site for peripheral blood eosinophil counts to 8. Changed study-stopping reason to reflect the occurrence of confirmed immune complex disease in a subject treated with benralizumab. Changes in inclusion and exclusion criteria. Added that a major deviation from the study protocol as judged by the investigator and/or the sponsor a reason for withdrawal. Modified procedures for following subjects for safety who were permanently discontinued from receiving investigational product. Changed procedures to allow for replacement of subjects who had not met major eligibility criteria and were withdrawn after receiving at least one dose of investigational product in error. Specified 21-gauge needle to be used. Specified when investigational product should not be administered. Updated text describing medium and high doses of ICS/LABA combination inhalers; added that subjects on high-dose ICS/LABA who used a secondary ICS inhaler were to be classified as high-dose subjects. Text describing rescreening procedures was modified. Removed sentence and reference citation regarding minimally clinical important difference in the TNSS-3. Changed the significance level to 0.2; changed the two-sided confidence interval to 80%; changed the sample size of the eosinophil-positive cohort and provided justification to augment the probability that the primary objective of detecting a reduction in asthma exacerbations in active versus placebo with adequate statistical power will be achieved; updated references as needed.

16 July 2012	Added section describing potential reason for stopping study for futility. Added interim analysis and a section describing unblinding for the interim analysis. Changed references to Week 52 analysis to Stage I analysis; Clarified the Stage I and Stage II analyses that will be conducted. Changed the primary endpoint analysis from Cochran-Mantel-Haenszel method to Poisson regression with overdispersion adjustment factor. Cochran-Mantel- Haenszel and negative binomial regression were considered sensitivity analyses. Removed weighted mean rate of asthma exacerbations as an exploratory endpoint.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported