Clinical trial results:
A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase IIIb Study to Evaluate the Safety and Efficacy of Benralizumab 30 mg sc in Patients with Severe Asthma Uncontrolled on Standard of Care Treatment (ANDHI)

Summary

EudraCT number	2017-001040-35
Trial protocol	DK GB FR BE SE NL AT ES FI IT
Global end of trial date	21 October 2020

Results information

Result version number	v1 (current)
This version publication date	03 November 2021
First version publication date	03 November 2021

Trial information

Trial identification

Sponsor protocol code	D3250C00045

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03170271
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Södertälje, Södertälje, Sweden, SE 151 85
Public contact	Global Clinical Lead, AstraZeneca, +1 8772409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 8772409479, information.center@astrazeneca.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 September 2019

Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	21 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The goal of this study was to evaluate the efficacy and safety of repeat dosing of benralizumab 30 milligrams (mg), administered subcutaneously (sc), compared to placebo on top of standard of care asthma therapy in patients with severe uncontrolled asthma.

The primary objective was to determine the effect of benralizumab on the rate of asthma exacerbations (treatment period 24 weeks).

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation / Good Clinical Practice, applicable regulatory requirements, and the AstraZeneca policy on Bioethics.

Background therapy:

Patients with a history of physician-diagnosed asthma must have been on treatment with medium-to-high dose inhaled corticosteroids (ICS) plus asthma controller, for at least 12 months prior to enrolment. Other acceptable asthma controllers included a long-acting bronchodilator, a leukotriene inhibitor, theophylline preparations or maintenance oral corticosteroids (OCS; maximum total daily dose 20 mg prednisone or equivalent).

Evidence for comparator: -

Actual start date of recruitment	07 July 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 221
Country: Number of subjects enrolled	Canada: 27
Country: Number of subjects enrolled	Italy: 109
Country: Number of subjects enrolled	France: 72
Country: Number of subjects enrolled	Spain: 68
Country: Number of subjects enrolled	United Kingdom: 47
Country: Number of subjects enrolled	Germany: 44
Country: Number of subjects enrolled	Sweden: 20
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Norway: 2
Worldwide total number of subjects	656
EEA total number of subjects	361

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)	529
From 65 to 84 years	127
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with severe uncontrolled asthma and peripheral blood eosinophil counts of ≥150 cells/microliter (µL) (with major subgroups of 150–300 cells/µL plus clinical features and ≥300 cells/µL) were recruited to 221 centers in 14 countries. Patients were randomized 2:1 to benralizumab or placebo. Results are reported for the double-blind period.

Pre-assignment

Screening details:

Severe eosinophilic patients were to have had ≥2 asthma exacerbations while on maintenance ICS plus another asthma controller requiring treatment with systemic corticosteroids in the 12 months prior to enrolment. 660 patients were randomized but 4 patients were withdrawn after randomization as screen failures. Thus, 656 patients received treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Benralizumab

Arm description:

Patients received benralizumab 30 mg administered sc in an accessorized pre-filled syringe at Week 0 (initial dose), Week 4 (loading dose), Week 8 and Week 16. An End of Treatment (EOT) visit was performed at Week 24.

Arm type	Experimental
Investigational medicinal product name	Benralizumab
Investigational medicinal product code	MEDI-563
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Benralizumab 30 mg/milliliter (mL) solution for injection in an accessorized pre-filled syringe, 1 mL fill volume.

Arm title	Placebo

Arm description:

Patients received matching placebo solution administered sc in an accessorized pre-filled syringe at Week 0 (initial dose), Week 4 (loading dose), Week 8 and Week 16. An EOT visit was performed at Week 24.

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

Dosage and administration details:

Matching placebo solution for injection in an accessorized pre-filled syringe, 1 mL fill volume.

Number of subjects in period 1	Benralizumab	Placebo
Started	427	229
Full Analysis Set (FAS)	427	229
Completed	398	218
Not completed	29	11
Physician decision	1	-
Protocol-specified withdrawal criterion	2	1
Adverse event, non-fatal	7	2
Unspecified	2	2
Consent withdrawn by subject	17	5
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Benralizumab
Reporting group description:	
Patients received benralizumab 30 mg administered sc in an accessorized pre-filled syringe at Week 0 (initial dose), Week 4 (loading dose), Week 8 and Week 16. An End of Treatment (EOT) visit was performed at Week 24.	
Reporting group title	Placebo
Reporting group description:	
Patients received matching placebo solution administered sc in an accessorized pre-filled syringe at Week 0 (initial dose), Week 4 (loading dose), Week 8 and Week 16. An EOT visit was performed at Week 24.	

Reporting group values	Benralizumab	Placebo	Total
Number of subjects	427	229	656
Age categorical Units: subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	345	184	529
From 65-84 years	82	45	127
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	52.5	53.3	
standard deviation	± 12.69	± 12.52	-
Sex: Female, Male Units: subjects			
Female	263	136	399
Male	164	93	257
Race Units: Subjects			
White	314	168	482
Black or African American	35	18	53
Asian	11	7	18
Native Hawaiian or other Pacific Islander	0	1	1
Other	5	2	7
Missing	62	33	95
Ethnicity Units: Subjects			
Hispanic or Latino	49	25	74
Not Hispanic or Latino	318	172	490
Unknown or Not Reported	60	32	92

Screening eosinophil count group (cells/µL) Units: Subjects			
≥ 150 – < 300	129	63	192
≥ 300	297	165	462
Missing	1	1	2
Baseline eosinophil count group (cells/µL) Units: Subjects			
< 300	146	74	220
≥ 300 – < 450	105	56	161
≥ 450	176	99	275

End points

End points reporting groups

Reporting group title	Benralizumab
Reporting group description:	
Patients received benralizumab 30 mg administered sc in an accessorized pre-filled syringe at Week 0 (initial dose), Week 4 (loading dose), Week 8 and Week 16. An End of Treatment (EOT) visit was performed at Week 24.	
Reporting group title	Placebo
Reporting group description:	
Patients received matching placebo solution administered sc in an accessorized pre-filled syringe at Week 0 (initial dose), Week 4 (loading dose), Week 8 and Week 16. An EOT visit was performed at Week 24.	

Primary: Annualized Rate of Asthma Exacerbations Over the Treatment Period (up to Week 24)

End point title	Annualized Rate of Asthma Exacerbations Over the Treatment Period (up to Week 24)
End point description:	
An asthma exacerbation was defined as a worsening of asthma that led to any of the following: • Use of systemic corticosteroids (or temporary increase in stable OCS background dose) for ≥3 days; a single depo-injectable dose of corticosteroids was considered equivalent to a 3-day course of systemic corticosteroids. • An emergency room/urgent care visit (defined as evaluation and treatment for <24 hours in emergency department or urgent care center) due to asthma that required systemic corticosteroids (as per above). • An inpatient hospitalization (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma. Annual exacerbation rate=365.25*total number of exacerbations/total duration of follow-up within treatment group. Annual asthma exacerbation rate over the 24-week period was estimated using a negative binomial model. The FAS included all randomized patients who received ≥1 dose of investigational product (IP).	
End point type	Primary
End point timeframe:	
Baseline (Week 0) up to Week 24	

End point values	Benralizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	427	229		
Units: Events/year				
number (confidence interval 95%)	0.94 (0.79 to 1.12)	1.86 (1.54 to 2.24)		

Statistical analyses

Statistical analysis title	Comparison between treatments
Statistical analysis description:	
Comparison of annual exacerbation rates for benralizumab versus (vs) placebo (rate ratio). Treatment	

group, region, number of exacerbations in previous year and maintenance OCS use at baseline were included in the negative binomial model as covariates. The log of each patient's corresponding follow-up time was used as an offset variable in the model to adjust for patients having different follow-up times during which events occurred.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	656
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.65

Notes:

[1] - The null hypothesis was that the exacerbation rate of benralizumab was equal to the exacerbation rate of placebo.

Secondary: Change from Baseline in Saint George Respiratory Questionnaire (SGRQ) Total Score to the EOT (Week 24)

End point title	Change from Baseline in Saint George Respiratory Questionnaire (SGRQ) Total Score to the EOT (Week 24)

End point description:

The SGRQ is a 50-item patient-reported outcome instrument which measures the health status of patients with airway obstruction diseases. The questionnaire is divided into 2 parts: part 1 consists of 8 items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition. The SGRQ total score indicates the impact of disease on overall health status and is expressed as a percentage of overall impairment (scores range from 0 to100, with 100 representing worst possible health status and 0 indicating the best possible health status). The least squares (LS) mean change from baseline in SGRQ total score at Week 24 is presented. The FAS included all randomized patients who received ≥1 dose of IP.

End point type	Secondary

End point timeframe:

Baseline (Week 0) and Week 24

End point values	Benralizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	364	204		
Units: Scores on a scale				
least squares mean (standard error)	-23.06 (± 1.00)	-14.94 (± 1.34)		

Statistical analyses

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Change from baseline in SGRQ total score at Week 24 was compared between the benralizumab group and placebo group using a restricted maximum likelihood based on a mixed-effect model for repeated measures (MMRM) analysis.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	568
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	-8.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.41
upper limit	-4.82

Notes:

[2] - Model: Change from baseline in SGRQ total score = Treatment + baseline SGRQ total score + region + number of exacerbations in previous year + maintenance OCS use at baseline + visit + treatment by visit.

Secondary: Change from Baseline in Pre-Bronchodilator (BD) Forced Expiratory Volume in First Second (FEV1) to the EOT (Week 24)

End point title	Change from Baseline in Pre-Bronchodilator (BD) Forced Expiratory Volume in First Second (FEV1) to the EOT (Week 24)

End point description:

Lung function was assessed by FEV1 which was measured by spirometry. Spirometry was performed by the Investigator or authorized delegate according to American Thoracic Society/European Respiratory Society guidelines. The LS mean change from baseline in pre-BD FEV1 at Week 24 is presented. The FAS included all randomized patients who received ≥1 dose of IP.

End point type	Secondary

End point timeframe:

Baseline (Week 0) and Week 24

End point values	Benralizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	213		
Units: Liters (L)				
least squares mean (standard error)	0.30 (± 0.02)	0.14 (± 0.03)		

Statistical analyses

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Change from baseline in pre-BD FEV1 at Week 24 was compared between the benralizumab group and placebo group using a restricted maximum likelihood based on a MMRM analysis.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	606
Analysis specification	Pre-specified

Analysis type	superiority[3]
P-value	< 0.0001
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.23

Notes:

[3] - Model: Change from baseline in pre-BD FEV1 = Treatment + baseline pre-BD FEV1 + region + number of exacerbations in previous year + maintenance OCS use at baseline + gender + age + visit + treatment by visit.

Secondary: Change from Baseline in Asthma Control Questionnaire 6 (ACQ-6) Score to the EOT (Week 24)

End point title	Change from Baseline in Asthma Control Questionnaire 6 (ACQ-6) Score to the EOT (Week 24)

End point description:

The ACQ-6 is a shortened version of the ACQ that assesses asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath and wheezing) and short-acting β-2 receptor agonist use. Patients were asked to recall the status of their asthma during the previous week and respond to the questions of the ACQ-6 on a 7-point scale. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is computed as the mean of the responses from all the items in the questionnaire. Mean scores of ≤0.75 indicated well-controlled asthma, scores between 0.75 and <1.5 indicated partly-controlled asthma, and a score ≥1.5 indicated not well-controlled asthma. The LS mean change from baseline in ACQ-6 score at Week 24 is presented. The FAS included all randomized patients who received ≥1 dose of IP.

End point type	Secondary

End point timeframe:

Baseline (Week 0) and Week 24

End point values	Benralizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	216		
Units: Scores on a scale				
least squares mean (standard error)	-1.47 (± 0.06)	-1.01 (± 0.08)		

Statistical analyses

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Change from baseline in ACQ-6 score at Week 24 was compared between the benralizumab group and placebo group using a restricted maximum likelihood based on a MMRM analysis.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	609
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.0001

Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.65
upper limit	-0.27

Notes:

[4] - Model: Change from baseline in ACQ-6 score = Treatment + baseline ACQ-6 score + region + number of exacerbations in previous year + maintenance OCS use at baseline + visit + treatment by visit.

Secondary: Time to First Asthma Exacerbation (up to Week 24)

End point title	Time to First Asthma Exacerbation (up to Week 24)

End point description:

Time to first asthma exacerbation was derived as follows:
Start date of first asthma exacerbation − Date of randomization + 1.
The time to first asthma exacerbation for patients who did not experience an asthma exacerbation during the treatment period was censored at the EOT visit (Week 24) for patients who completed the study. Patients who withdrew from the study or were lost to follow-up before the EOT visit were censored at the last visit date after which an exacerbation could not be assessed. The median time to first asthma exacerbation was not calculated, so the number of patients who experienced an asthma exacerbation is presented for the measured values. The FAS included all randomized patients who received ≥1 dose of IP.

End point type	Secondary

End point timeframe:

Baseline (Week 0) up to Week 24

End point values	Benralizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	427	229		
Units: Patients	123	107		

Statistical analyses

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Comparison of time to first asthma exacerbation for benralizumab vs placebo. Treatment group, region, number of exacerbations in previous year and maintenance OCS use at baseline were included in the Cox proportional hazard model as covariates.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	656
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.52
Confidence interval	

level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.67

Notes:

[5] - A hazard ratio < 1 favours benralizumab to be associated with a longer time from randomization to the first exacerbation than placebo.

Secondary: Change from Run-in Baseline Home Peak Expiratory Flow (PEF) (Morning and Evening) to the EOT (Week 24)

End point title	Change from Run-in Baseline Home Peak Expiratory Flow (PEF) (Morning and Evening) to the EOT (Week 24)

End point description:

Home PEF testing was performed by the patient each morning after awakening and before taking their morning asthma medications, and each evening using a peak flow meter. Measurements were taken at approximately the same time each day and recorded in the Asthma Daily Diary. The maximum of the 3 measurements performed every morning and evening were used in the calculation of the weekly means. A weekly mean was calculated as the sum of all non-missing daily measures over the 7 sequential days divided by the number of non-missing daily measures. If more than 3 daily measures (> 50%) within a period were missing, then the weekly mean for that period was set to 'missing'. Change from run-in baseline in weekly means for morning PEF and evening PEF are presented. Baseline was the average for data collected over the last 7 days of the run-in period prior to randomization. The FAS included all randomized patients who received ≥1 dose of IP.

End point type	Secondary

End point timeframe:

Run-in baseline (from Day -28 to Day 0) and Week 24

End point values	Benralizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	427[6]	229[7]		
Units: L/minute				
least squares mean (standard error)				
Morning (n=276, 142)	27.17 (± 3.98)	7.06 (± 5.49)		
Evening (n=256, 144)	16.47 (± 4.04)	-6.61 (± 5.54)		

Notes:

[6] - 'n' in category title denotes number of patients analyzed for that category.

[7] - 'n' in category title denotes number of patients analyzed for that category.

Statistical analyses

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Change from run-in baseline in morning PEF at Week 24 was compared between the benralizumab group and placebo group using a restricted maximum likelihood based on a MMRM analysis.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	656
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.0031
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	20.11
Confidence interval	

level	95 %
sides	2-sided
lower limit	6.79
upper limit	33.44

Notes:

[8] - Model: Change from baseline in PEF = Treatment + baseline PEF + region + number of exacerbations in previous year + maintenance OCS use at baseline + visit + treatment by visit.

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Change from run-in baseline in evening PEF at Week 24 was compared between the benralizumab group and placebo group using a restricted maximum likelihood based on a MMRM analysis.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	656
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0008
Method	Repeated measures analysis
Parameter estimate	LS Mean Difference
Point estimate	23.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.62
upper limit	36.55

Notes:

[9] - Model: Change from baseline in PEF = Treatment + baseline PEF + region + number of exacerbations in previous year + maintenance OCS use at baseline + visit + treatment by visit.

Secondary: Change from Baseline in Short Form 36-item Health Survey, version 2 (SF-36v2) to the EOT (Week 24)

End point title	Change from Baseline in Short Form 36-item Health Survey, version 2 (SF-36v2) to the EOT (Week 24)

End point description:

The SF-36v2 is a quality of life scale comprising 8 domains of health status: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. The physical and mental health component summary scores are computed from subscale scores to give a broader metric of physical and mental health-related quality of life. Each domain score, as well as the physical and mental component scores, were scored on a scale from 0-100 (worst health possible to best health possible); higher scores indicate better health status. Norm-based scoring was used to calculate the 8 SF-36v2 subscales and the 2 component scores. The LS mean change from baseline in each of the SF-36 subscale and component summary scores at Week 24 are presented. The FAS included all randomized patients who received ≥1 dose of IP.

End point type	Secondary

End point timeframe:

Baseline (Week 0) and Week 24

End point values	Benralizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	287	169		
Units: Scores on a scale				
least squares mean (standard error)				
Physical functioning	17.76 (± 1.21)	12.42 (± 1.59)		
Role limitations due to physical health	17.62 (± 1.34)	10.82 (± 1.76)		
Bodily pain	6.44 (± 1.37)	3.37 (± 1.79)		
General health perceptions	12.92 (± 1.01)	7.29 (± 1.34)		
Vitality	12.04 (± 1.10)	6.53 (± 1.44)		
Social functioning	12.44 (± 1.34)	9.32 (± 1.75)		
Role limitations due to emotional problems	8.23 (± 1.18)	5.79 (± 1.55)		
Mental health	5.57 (± 0.90)	3.89 (± 1.18)		
Physical health component summary score	6.09 (± 0.46)	3.77 (± 0.60)		
Mental health component summary score	2.87 (± 0.48)	1.99 (± 0.64)		

Statistical analyses

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Change from baseline in SF-36v2 subscale score for physical functioning at Week 24 was compared between the benralizumab group and placebo group using a restricted maximum likelihood based on a MMRM analysis.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	456
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.0077
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	5.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.42
upper limit	9.28

Notes:

[10] - Model: Change from baseline in SF-36v2 score = Treatment + baseline SF-36v2 score + region + number of exacerbations in previous year + maintenance OCS use at baseline + visit + treatment by visit.

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Change from baseline in SF-36v2 subscale score for role limitations due to physical health at Week 24 was compared between the benralizumab group and placebo group using a restricted maximum likelihood based on a MMRM analysis.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	456
Analysis specification	Pre-specified

Analysis type	superiority[11]
P-value	= 0.0022
Method	Repeated measures analysis
Parameter estimate	LS Mean Difference
Point estimate	6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.45
upper limit	11.14

Notes:

[11] - Model: Change from baseline in SF-36v2 score = Treatment + baseline SF-36v2 score + region + number of exacerbations in previous year + maintenance OCS use at baseline + visit + treatment by visit.

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Change from baseline in SF-36v2 subscale score for bodily pain at Week 24 was compared between the benralizumab group and placebo group using a restricted maximum likelihood based on a MMRM analysis.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	456
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.1741
Method	Repeated measures analysis
Parameter estimate	LS Mean Difference
Point estimate	3.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.36
upper limit	7.5

Notes:

[12] - Model: Change from baseline in SF-36v2 score = Treatment + baseline SF-36v2 score + region + number of exacerbations in previous year + maintenance OCS use at baseline + visit + treatment by visit.

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Change from baseline in SF-36v2 subscale score for general health perceptions at Week 24 was compared between the benralizumab group and placebo group using a restricted maximum likelihood based on a MMRM analysis.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	456
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.0009
Method	Repeated measures analysis
Parameter estimate	LS Mean Difference
Point estimate	5.62
Confidence interval	
level	95 %
sides	2-sided

lower limit	2.32
upper limit	8.92

Notes:

[13] - Model: Change from baseline in SF-36v2 score = Treatment + baseline SF-36v2 score + region + number of exacerbations in previous year + maintenance OCS use at baseline + visit + treatment by visit.

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Change from baseline in SF-36v2 subscale score for vitality at Week 24 was compared between the benralizumab group and placebo group using a restricted maximum likelihood based on a MMRM analysis.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	456
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.0025
Method	Repeated measures analysis
Parameter estimate	LS Mean Difference
Point estimate	5.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.95
upper limit	9.08

Notes:

[14] - Model: Change from baseline in SF-36v2 score = Treatment + baseline SF-36v2 score + region + number of exacerbations in previous year + maintenance OCS use at baseline + visit + treatment by visit.

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Change from baseline in SF-36v2 subscale score for social functioning at Week 24 was compared between the benralizumab group and placebo group using a restricted maximum likelihood based on a MMRM analysis.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	456
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.1583
Method	Repeated measures analysis
Parameter estimate	LS Mean Difference
Point estimate	3.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.22
upper limit	7.46

Notes:

[15] - Model: Change from baseline in SF-36v2 score = Treatment + baseline SF-36v2 score + region + number of exacerbations in previous year + maintenance OCS use at baseline + visit + treatment by visit.

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Change from baseline in SF-36v2 subscale score for role limitations due to emotional problems at Week 24 was compared between the benralizumab group and placebo group using a restricted maximum likelihood based on a MMRM analysis.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	456
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.2103
Method	Repeated measures analysis
Parameter estimate	LS Mean Difference
Point estimate	2.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.38
upper limit	6.27

Notes:

[16] - Model: Change from baseline in SF-36v2 score = Treatment + baseline SF-36v2 score + region + number of exacerbations in previous year + maintenance OCS use at baseline + visit + treatment by visit.

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Change from baseline in SF-36v2 subscale score for mental health at Week 24 was compared between the benralizumab group and placebo group using a restricted maximum likelihood based on a MMRM analysis.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	456
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.2581
Method	Repeated measures analysis
Parameter estimate	LS Mean Difference
Point estimate	1.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.23
upper limit	4.59

Notes:

[17] - Model: Change from baseline in SF-36v2 score = Treatment + baseline SF-36v2 score + region + number of exacerbations in previous year + maintenance OCS use at baseline + visit + treatment by visit.

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Change from baseline in SF-36v2 physical health component summary score at Week 24 was compared between the benralizumab group and placebo group using a restricted maximum likelihood based on a MMRM analysis.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	456
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.0022
Method	Repeated measures analysis

Parameter estimate	LS Mean Difference
Point estimate	2.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	3.81

Notes:

[18] - Model: Change from baseline in SF-36v2 score = Treatment + baseline SF-36v2 score + region + number of exacerbations in previous year + maintenance OCS use at baseline + visit + treatment by visit.

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Change from baseline in SF-36v2 mental health component summary score at Week 24 was compared between the benralizumab group and placebo group using a restricted maximum likelihood based on a MMRM analysis.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	456
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.2751
Method	Repeated measures analysis
Parameter estimate	LS Mean Difference
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	2.44

Notes:

[19] - Model: Change from baseline in SF-36v2 score = Treatment + baseline SF-36v2 score + region + number of exacerbations in previous year + maintenance OCS use at baseline + visit + treatment by visit.

Secondary: Patient Global Impression of Severity (PGI-S): Responder Status at the EOT (Week 24)

End point title	Patient Global Impression of Severity (PGI-S): Responder Status at the EOT (Week 24)

End point description:

The PGI-S is a single question asking the patient to rate the overall severity of their symptoms using a 6-point categorical response scale from 0 to 5 where 0=no symptoms and 5=very severe symptoms. Higher scores indicate a worse outcome. Improvement was defined as a PGI-S at EOT (Week 24) better than PGI-S at baseline. Important improvement was defined as PGI-S at baseline = moderate symptoms or severe symptoms or very severe symptoms shifting to PGI-S at EOT = no symptoms or very mild symptoms or mild symptoms. Patients with missing data at the EOT visit who did not complete the study were considered non-responders. For patients who completed the study with missing data at EOT (Week 24), their last evaluable post-baseline score was used to define responder status. The percentage of patients for each of the indicated PGI-S responder categories are presented. The FAS included all randomized patients who received ≥1 dose of IP.

End point type	Secondary

End point timeframe:

Baseline (Week 0) and Week 24

End point values	Benralizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	345	187		
Units: Percentage of patients				
number (not applicable)				
Improvement	61.7	53.5		
Important improvement	45.5	38.0		

Statistical analyses

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Estimate of the log odds of being a responder classified as type 'Important Improvement' at Week 24 in the benralizumab group compared to the placebo group using a logistic regression.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.0401
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	2.16

Notes:

[20] - Model: ln (1/(1-p)) = Treatment + baseline score + region + number of exacerbations in previous year + maintenance OCS use at baseline, where p is the proportion of patients being a responder.

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Estimate of the log odds of being a responder classified as type 'Improvement' at Week 24 in the benralizumab group compared to the placebo group using a logistic regression.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.0233
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	2.25

Notes:

[21] - Model: ln (1/(1-p)) = Treatment + baseline score + region + number of exacerbations in previous year + maintenance OCS use at baseline, where p is the proportion of patients being a responder.

Secondary: Clinician Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C): Responder Status at the EOT (Week 24)

End point title	Clinician Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C): Responder Status at the EOT (Week 24)

End point description:

The Investigator and the patient were asked separately to rate the degree of change in the overall asthma status compared to the start of treatment, i.e. baseline visit. A 7-point rating scale was used for CGI-C (rated by Investigator) and PGI-C (rated by patient) where: 1=Very Much Improved; 2=Much Improved; 3=Minimally Improved; 4=No Changes; 5=Minimally Worse; 6=Much Worse, and 7=Very Much Worse. Higher scores indicate a worse outcome. Responder category definitions: Much improved=(Much improved, Very much improved); Very much improved=(Very much improved). Patients with missing data at the EOT visit who did not complete the study were considered non-responders. For patients who completed the study with missing data at EOT (Week 24), their last evaluable post-baseline score was used to define responder status. The percentage of patients for each of the indicated CGI-C and PGI-C responder categories are presented. The FAS included all randomized patients who received ≥1 dose of IP.

End point type	Secondary

End point timeframe:

Baseline (Week 0) and Week 24

End point values	Benralizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	427[22]	229[23]		
Units: Percentage of patients				
number (not applicable)				
CGI-C: Much improved (n=420, 227)	52.9	35.2		
CGI-C: Very much improved (n=420, 227)	15.0	4.8		
PGI-C: Much improved (n=424, 228)	55.9	38.2		
PGI-C: Very much improved (n=424, 228)	37.7	16.7		

Notes:

[22] - 'n' in category title denotes number of patients analyzed for that category.

[23] - 'n' in category title denotes number of patients analyzed for that category.

Statistical analyses

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Estimate of the log odds of being a CGI-C responder classified as type 'Much improved' at Week 24 in the benralizumab group compared to the placebo group using a logistic regression.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	656
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.47
upper limit	2.86

Notes:

[24] - Model: ln (1/(1-p)) = Treatment + region + number of exacerbations in previous year + maintenance OCS use at baseline, where p is the proportion of patients being a responder.

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Estimate of the log odds of being a CGI-C responder classified as type 'Very much improved' at Week 24 in the benralizumab group compared to the placebo group using a logistic regression.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	656
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.0003
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.77
upper limit	6.7

Notes:

[25] - Model: ln (1/(1-p)) = Treatment + region + number of exacerbations in previous year + maintenance OCS use at baseline, where p is the proportion of patients being a responder.

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Estimate of the log odds of being a PGI-C responder classified as type 'Much improved' at Week 24 in the benralizumab group compared to the placebo group using a logistic regression.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	656
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.48
upper limit	2.87

Notes:

[26] - Model: ln (1/(1-p)) = Treatment + region + number of exacerbations in previous year + maintenance OCS use at baseline, where p is the proportion of patients being a responder.

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Estimate of the log odds of being a PGI-C responder classified as type 'Very much improved' at Week 24 in the benralizumab group compared to the placebo group using a logistic regression.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	656
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.02
upper limit	4.51

Notes:

[27] - Model: ln (1/(1-p)) = Treatment + region + number of exacerbations in previous year + maintenance OCS use at baseline, where p is the proportion of patients being a responder.

Secondary: Change from Baseline in Predominant Symptom and Impairment Assessment (PSIA) Severity Score for Average of Top 3 Ranked Symptoms/Impairments and for Top Ranked Symptom/Impairment at the EOT (Week 24)

End point title	Change from Baseline in Predominant Symptom and Impairment Assessment (PSIA) Severity Score for Average of Top 3 Ranked Symptoms/Impairments and for Top Ranked Symptom/Impairment at the EOT (Week 24)

End point description:

For part 1 of the PSIA only administered at baseline, patients reviewed 8 concepts (including cardinal asthma symptoms, activities, awakenings, triggers) and selected those which were typically bothersome. Based on part 1 selections, part 2 of the PSIA produced a rank ordered list of bothersome concepts individualized per the patient for subsequent evaluation. For part 3 of the PSIA assessed at baseline and during the study, patients recorded the severity of each selected symptom or impairment using an 11-point numeric rating scale where: 0=Did not experience and 10=Worst I can imagine. The LS mean change from baseline in PSIA severity score for the indicated categories at Week 24 are presented. A negative change from baseline indicates an improvement in symptoms. Note: Average PSIA was calculated only where all of top 3 ranked symptoms/impairments were available, otherwise average was set to missing. The FAS included all randomized patients who received ≥1 dose of IP.

End point type	Secondary

End point timeframe:

Baseline (Week 0) and Week 24

End point values	Benralizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	319[28]	180[29]		
Units: Scores on a scale				
least squares mean (standard error)				
Average of top 3 ranked (n=302, 172)	-2.97 (± 0.14)	-1.82 (± 0.19)		
Top ranked (n=319, 180)	-3.02 (± 0.15)	-1.87 (± 0.20)		

Notes:

[28] - 'n' in category title denotes number of patients analyzed for that category.

[29] - 'n' in category title denotes number of patients analyzed for that category.

Statistical analyses

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Change from baseline in PSIA severity score of top ranked symptom/impairment at Week 24 was compared between the benralizumab group and placebo group using a restricted maximum likelihood based on a MMRM analysis.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	< 0.0001
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	-1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.64
upper limit	-0.66

Notes:

[30] - Model: Change from baseline in PSIA score (top ranked) =Treatment + baseline PSIA score (top ranked) + region + number of exacerbations in previous year + maintenance OCS use at baseline + visit + treatment by visit.

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Change from baseline in PSIA severity score for the average of top 3 ranked symptoms/impairments at Week 24 was compared between the benralizumab group and placebo group using a restricted maximum likelihood based on a MMRM analysis.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	< 0.0001
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	-1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.62
upper limit	-0.68

Notes:

[31] - Model: Change from baseline in average PSIA score (top 3 ranked) =Treatment + baseline average PSIA score (top 3 ranked) + region + number of exacerbations in previous year + maintenance OCS use at baseline + visit + treatment by visit.

Secondary: Change From Baseline in the Sino-Nasal Outcome Test Item 22 (SNOT-22) Total Score to the EOT (Week 24)

End point title	Change From Baseline in the Sino-Nasal Outcome Test Item 22 (SNOT-22) Total Score to the EOT (Week 24)

End point description:

The 22-item SNOT 22 questionnaire was used to assess the rhinosinusitis health status and quality of life of patients with baseline chronic rhinosinusitis with nasal polyposis. The 22-question SNOT-22 is scored as 0 (no problem) to 5 (problem as bad as it can be) with a total range from 0 to 110. Higher

scores indicate poorer outcomes. The LS mean changes from baseline in SNOT-22 total score in patients in the chronic rhinosinusitis with nasal polyposis sub-study analysis set at Week 24 are presented. The chronic rhinosinusitis with nasal polyposis sub-study analysis set was defined as the subset of patients with doctor-diagnosed chronic rhinosinusitis and nasal polyposis included in their medical history who had signed the informed consent to participate in the sub-study and who had received ≥1 dose of IP.

End point type	Secondary

End point timeframe:

Baseline (Week 0) and Week 24

End point values	Benralizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	50		
Units: Scores on a scale				
least squares mean (standard error)	-19.02 (± 2.27)	-10.11 (± 3.04)		

Statistical analyses

Statistical analysis title	Comparison between treatments

Statistical analysis description:

Change from baseline in SNOT-22 total score at Week 24 was compared between the benralizumab group and placebo group using a restricted maximum likelihood based on a MMRM analysis.

Comparison groups	Benralizumab v Placebo
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority[32]
P-value	= 0.0204
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	-8.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.42
upper limit	-1.4

Notes:

[32] - Model: Change from baseline in SNOT-22 total score = Treatment + baseline SNOT-22 total score + region + number of exacerbations in previous year + maintenance OCS use at baseline + visit + treatment by visit.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event (AE) data is reported for the on-treatment period + follow-up (up to a maximum of 24 weeks). Assessed until 12 Sep 2019 analysis cut-off date for completion of the double-blind period of the study.

Adverse event reporting additional description:

AE definition for on-treatment period: onset date ≥ first dose of IP and ≤ scheduled EOT visit, or IP discontinuation visit for patients prematurely discontinuing IP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Patients received matching placebo solution administered sc in an accessorized pre-filled syringe at Week 0 (initial dose), Week 4 (loading dose), Week 8 and Week 16. An EOT visit was performed at Week 24.

Reporting group title	Benralizumab

Reporting group description:

Patients received benralizumab 30 mg administered sc in an accessorized pre-filled syringe at Week 0 (initial dose), Week 4 (loading dose), Week 8 and Week 16. An EOT visit was performed at Week 24.

Serious adverse events	Placebo	Benralizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 229 (10.92%)	23 / 427 (5.39%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma in situ			
subjects affected / exposed	1 / 229 (0.44%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anti-neutrophil cytoplasmic antibody positive vasculitis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytokine release syndrome			
subjects affected / exposed	0 / 229 (0.00%)	1 / 427 (0.23%)	

occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	0 / 229 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 229 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 229 (0.44%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	9 / 229 (3.93%)	9 / 427 (2.11%)	
occurrences causally related to treatment / all	0 / 11	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 229 (0.44%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 229 (0.44%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 229 (0.87%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 229 (0.44%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 229 (0.44%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Mydriasis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Food poisoning			
subjects affected / exposed	0 / 229 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 229 (0.44%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 229 (0.00%)	1 / 427 (0.23%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 229 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Costochondritis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 229 (0.44%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 229 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 229 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	1 / 229 (0.44%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypokalaemia			
subjects affected / exposed	1 / 229 (0.44%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 229 (0.44%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 229 (0.44%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 229 (0.87%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 229 (0.44%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 229 (0.44%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Benralizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	78 / 229 (34.06%)	136 / 427 (31.85%)	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 229 (5.68%)	14 / 427 (3.28%)	
occurrences (all)	17	16	
Dyspnoea			
subjects affected / exposed	13 / 229 (5.68%)	7 / 427 (1.64%)	
occurrences (all)	19	9	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 229 (3.06%)	37 / 427 (8.67%)	
occurrences (all)	11	50	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 229 (2.18%)	26 / 427 (6.09%)	
occurrences (all)	8	29	
Infections and infestations			
Bronchitis			
subjects affected / exposed	18 / 229 (7.86%)	22 / 427 (5.15%)	
occurrences (all)	22	23	
Nasopharyngitis			
subjects affected / exposed	17 / 229 (7.42%)	30 / 427 (7.03%)	
occurrences (all)	23	36	
Upper respiratory tract infection			
subjects affected / exposed	12 / 229 (5.24%)	17 / 427 (3.98%)	
occurrences (all)	13	19	
Sinusitis			
subjects affected / exposed	12 / 229 (5.24%)	28 / 427 (6.56%)	
occurrences (all)	17	32	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 January 2018	The protocol was amended to: • Reduce the total estimated number of patients to be randomized and sample size estimate; the change preserved number of patients receiving benralizumab and reduced number exposed to placebo, while retaining statistical power to detect a treatment difference for both asthma exacerbation reduction and SGRQ improvement. • Update inclusion criteria to specify additional indicators of variable lung function and to allow inclusion of patients with blood eosinophil count of ≥150 to <300 cells/µL (if they met other required clinical criteria at time of enrolment). • Update eligibility criteria assessed at Visit 4 to allow randomization of patients with either a pre-BD FEV1 that remained <80% of predicted, or that was not increased from the qualifying pre-BD FEV1 value at Visit 2 by more than 20%. • Reduce interim biomarker assessments. • Add rationale text for Sino-Nasal Outcome Test 22 Item.
18 July 2018	The protocol was amended for inclusion of a 56-week open-label ANDHI in-Practice (AiP) sub-study. Applicable sections were updated throughout the study protocol.
01 May 2020	The protocol was amended to: • Provide more recent Global Initiative for Asthma step guidelines. • Update the main outcome measures and supportive measures for the AiP sub-study to better characterize the extent of reduction in asthma controller medications, provide further information on the type and extent of background medication that has been reduced, to provide predictive baseline characteristics of patients who were unlikely to achieve medication reductions and those likely to achieve meaningful reduction, and to include patients receiving OCS in reduction analyses. • Define 2 additional efficacy analysis sets for inclusion of patients receiving OCS in reduction analyses and patients transitioning directly from ANDHI main study to ANDHI IP sub-study. • Add text to address the possible need for alternative study conduct procedures due to COVID-19.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported