Clinical trial results:
A Multicenter, Randomized, Double-blind, Parallel Group, Placebo controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Benralizumab in Adult Patients with Mild to Moderate Persistent Asthma

Summary

EudraCT number	2014-004427-40
Trial protocol	SK DE HU
Global end of trial date	07 October 2015

Results information

Result version number	v1 (current)
This version publication date	15 October 2016
First version publication date	15 October 2016

Trial information

Trial identification

Sponsor protocol code	D3250C00032

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02322775
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca Research and Development
Sponsor organisation address	One MedImmune Way, Gaithersburg, United States, MD 20878
Public contact	Mitchell Goldman, Global Clinical Leader Benralizumab, AstraZeneca Research and Development, +1 301 398 0323, Mitchell.Goldman@astrazeneca.com
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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	03 February 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to evaluate the effect of benralizumab on pulmonary function in mild to moderate asthmatic patients.

Protection of trial subjects:

The Informed Consent Form (ICF) incorporated or, in some cases, was accompanied by a separate document incorporating wording that complies with relevant data protection and privacy legislation.
The Principal Investigator(s) at each study center ensured:
• Each patient or legal guardian was given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study (before any study procedures were performed) as per local requirements. The ICF needed to be adjusted as per local requirements.
• Each patient or legal guardian was notified that they were free to discontinue from the study at any time.
• That each patient or legal guardian was given the opportunity to ask questions and allowed time to consider the information provided.
• Each patient or legal guardian provides signed and dated Informed Consent before conducting any procedure specifically for the study.
• The original, signed Informed Consent(s) was/were stored in the Investigator's Study File and kept for a period that is complaint with GCP/local regulatory requirements, whichever is longer.
• A copy of the signed Informed Consent Form was given to the patient.
• That any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation were described in the Informed Consent Form that is approved by an Ethics Committee.

Background therapy:

At the time of screening/run-in, all patients, irrespective of their previous background therapy, were converted to either 180 or 200 µg dry powder inhaler twice daily (based on what was approved in the country where the study site was located) for the duration of the study.
Changes to the patient's background controller regimen were discouraged during the study unless judged medically necessary by the Investigator; such changes were discussed with the AstraZeneca Study Physician. All changes in the patient's background medication were documented in source along with rational for change and recorded in eCRF.

Evidence for comparator:

Matching placebo solution for injection in an accessorized pre-filled syringe (PFS) was administered at the study center subcutaneously every 4 weeks for 3 doses (Week 0, Week 4, and Week 8).

Actual start date of recruitment	02 February 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Germany: 57

Country: Number of subjects enrolled	Hungary: 40
Country: Number of subjects enrolled	Poland: 25
Country: Number of subjects enrolled	Slovakia: 19
Country: Number of subjects enrolled	United States: 52
Worldwide total number of subjects	211
EEA total number of subjects	141

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)	182
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

After enrollment, eligible patients entered a 2- to 4-week screening/run-in period and were converted to budesonide dry powder inhaler twice daily for the duration of the study.
Patients who continued to meet eligibility criteria at the end of the run-in period entered a 12 weeks double-blind treatment period followed by two follow-up visits.

Pre-assignment

Screening details:

Eligible adult patients were stratified by baseline blood eosinophil count (<300 cells/µL or ≥300 cells/µL) and by region (USA versus Rest of the World per the IVRS). Patients were then randomized to either benralizumab 30 mg Q4W or placebo in a 1:1 ratio. 351 patients were enrolled (informed consent received) and 211 were randomized.

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, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Benralizumab 30 mg Q4W

Arm description:

Benralizumab administered subcutaneously every 4 weeks

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

Dosage and administration details:

Benralizumab 30 mg/mL solution for injection administered at the study center SC every 4 weeks for 3 doses

Arm title	Placebo

Arm description:

Placebo administered subcutaneously every 4 weeks

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 administered at the study center SC every 4 weeks for 3 doses

Number of subjects in period 1	Benralizumab 30 mg Q4W	Placebo
Started	106	105
Completed	101	99
Not completed	5	6
Consent withdrawn by subject	3	4
Not willing to perform all FU visits	-	1
Adverse event, non-fatal	1	-
Lost to follow-up	-	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Benralizumab 30 mg Q4W
Reporting group description: Benralizumab administered subcutaneously every 4 weeks	
Reporting group title	Placebo
Reporting group description: Placebo administered subcutaneously every 4 weeks	

Reporting group values	Benralizumab 30 mg Q4W	Placebo	Total
Number of subjects	106	105	211
Age categorical Units: Subjects			
Adults (18-64 years)	92	90	182
From 65-75 years	14	15	29
Age Continuous | Units: Years			
arithmetic mean	48.3	51.1	
standard deviation	± 14.4	± 12.6	-
Gender, Male/Female Units: Participants			
Female	62	67	129
Male	44	38	82
Age, Customized Units: Subjects			
>=18-<50	49	44	93
>=50-<65	43	46	89
>=65-<=75	14	15	29
Race/Ethnicity, Customized Units: Subjects			
Asian	1	0	1
Black or African American	7	4	11
White	98	99	197
Other	0	2	2
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	6	3	9
Not Hispanic or Latino	100	102	202

End points

End points reporting groups

Reporting group title	Benralizumab 30 mg Q4W
Reporting group description:	
Benralizumab administered subcutaneously every 4 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo administered subcutaneously every 4 weeks	

Primary: Change from baseline in pre-bronchodilator forced expiratory volume in 1 second (FEV1) (L) at Week 12

End point title	Change from baseline in pre-bronchodilator forced expiratory volume in 1 second (FEV1) (L) at Week 12
End point description:	
The changes from baseline in pre-bronchodilator FEV1 (L) are compared between benralizumab 30 mg Q4W and placebo by using the mixed-effect repeated measures (MMRM) with baseline blood eosinophil count (≥300 cells/µL or <300 cells/µL), protocol specified visit (Week 4, Week 8, Week 12), region (Europe or North America) and treatment*visit interaction as fixed effects and baseline pre-bronchodilator FEV1 (L) as a covariate.	
End point type	Primary
End point timeframe:	
Up to Week 12	

End point values	Benralizumab 30 mg Q4W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102[1]	104[2]		
Units: Litre				
arithmetic mean (standard deviation)				
Baseline	2.248 (± 0.6062)	2.246 (± 0.7677)		
Week 12	2.31 (± 0.6702)	2.261 (± 0.7959)		
Change from baseline at Week 12	0.057 (± 0.2734)	-0.016 (± 0.235)		

Notes:

[1] - Number of subjects analyzed is the number of subjects included in the MMRM analyses.

[2] - Number of subjects analyzed is the number of subjects included in the MMRM analyses.

Statistical analyses

Statistical analysis title	Treatment comparisons of CFB in pre-BD FEV1
Statistical analysis description:	
The null hypothesis was: H0: Change from baseline in pre-bronchodilator FEV1 (L) at Week 12 (benralizumab vs placebo)=0.	
Comparison groups	Benralizumab 30 mg Q4W v Placebo

Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04 [3]
Method	Mixed models analysis
Parameter estimate	Difference of Least Square Means
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.15

Notes:

[3] - Hypothesis testing were reported using 2-sided 5% level tests with nominal p-values (i.e., not adjusted for multiplicity).

Secondary: Change from baseline in morning peak expiratory flow (PEF) (L/min) at home at Week 12

End point title	Change from baseline in morning peak expiratory flow (PEF) (L/min) at home at Week 12

End point description:

Home morning PEF (L/min) weekly means were calculated using daily diary entries. The changes from baseline in weekly average of morning PEF (L/min) are compared between benralizumab 30 mg Q4W and placebo by using the mixed-effect model repeated measures (MMRM) with baseline blood eosinophil count (≥300 cells/µL or <300 cells/µL), protocol specified visit, region (Europe or North America) and treatment*visit interaction as fixed effects and baseline morning PEF (L/min) as a covariate.

End point type	Secondary

End point timeframe:

Up to Week 12

End point values	Benralizumab 30 mg Q4W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104[4]	104[5]		
Units: L/min				
arithmetic mean (standard deviation)				
Baseline	307.413 (± 95.9467)	308.226 (± 113.5895)		
Week 12	311.041 (± 101.8169)	304.037 (± 113.2538)		
Change from baseline at Week 12	1.675 (± 56.5182)	-6.196 (± 45.3077)		

Notes:

[4] - Number of subjects analyzed is the number of subjects included in the MMRM analyses.

[5] - Number of subjects analyzed is the number of subjects included in the MMRM analyses.

Statistical analyses

Statistical analysis title	Treatment comparisons of CFB in morning PEF
Comparison groups	Benralizumab 30 mg Q4W v Placebo

Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.233 [6]
Method	Mixed models analysis
Parameter estimate	Difference of Least Square Means
Point estimate	8.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.74
upper limit	23.42

Notes:

[6] - Hypothesis testing were reported using 2-sided 5% level tests with nominal p-values (i.e., not adjusted for multiplicity).

Secondary: Change from baseline in evening peak expiratory flow (PEF) (L/min) at home at Week 12

End point title	Change from baseline in evening peak expiratory flow (PEF) (L/min) at home at Week 12

End point description:

Home evening PEF (L/min) weekly means were calculated using daily diary entries. The outcome variable for evening PEF (L/min) was the change from baseline at Week 12 in weekly average of evening PEF (L/min). The changes are compared between benralizumab 30 mg Q4W and placebo by using the mixed-effect model repeated measures (MMRM) with baseline blood eosinophil count (≥300 cells/μL or <300 cells/μL), protocol specified visit, region (Europe or North America) and treatment*visit interaction as fixed effects and baseline evening PEF (L/min) as a covariate.

End point type	Secondary

End point timeframe:

Up to Week 12

End point values	Benralizumab 30 mg Q4W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104[7]	105[8]		
Units: L/min				
arithmetic mean (standard deviation)				
Baseline	326.948 (± 97.4034)	316.743 (± 116.6919)		
Week 12	330.719 (± 106.7579)	316.047 (± 118.7)		
Change from baseline at Week 12	1.361 (± 51.9979)	-2.956 (± 47.9136)		

Notes:

[7] - Number of subjects analyzed is the number of subjects included in the MMRM analyses.

[8] - Number of subjects analyzed is the number of subjects included in the MMRM analyses.

Statistical analyses

Statistical analysis title	Treatment comparisons of CFB in evening PEF
Comparison groups	Benralizumab 30 mg Q4W v Placebo

Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.456 [9]
Method	Mixed models analysis
Parameter estimate	Difference of Least Square Means
Point estimate	5.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.67
upper limit	19.25

Notes:

[9] - Hypothesis testing were reported using 2-sided 5% level tests with nominal p-values (i.e., not adjusted for multiplicity).

Secondary: Change from baseline in total asthma symptom score at Week 12

End point title	Change from baseline in total asthma symptom score at Week 12

End point description:

Asthma symptoms were recorded by the patient each morning and evening in the asthma daily diary. Symptoms were recorded using a scale of 0-3, where 0 indicates no asthma symptoms. The daily asthma symptom total score was calculated by taking the sum of the daytime score recorded in the evening and the nighttime score recorded the following morning. The outcome variable for total asthma score was change from baseline at Week 12 in weekly total asthma score. The changes are compared between benralizumab 30 mg Q4W and placebo by using the mixed-effect model repeated measures (MMRM) with baseline blood eosinophil count (≥300 cells/μL or <300 cells/μL), protocol specified visit, region (Europe or North America) and treatment*visit interaction as fixed effects and baseline total asthma score as a covariate.

End point type	Secondary

End point timeframe:

Up to Week 12

End point values	Benralizumab 30 mg Q4W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104[10]	105[11]		
Units: Point scale				
arithmetic mean (standard deviation)				
Baseline	1.934 (± 0.931)	1.952 (± 1.0375)		
Week 12	1.326 (± 1.0448)	1.541 (± 1.1208)		
Change from baseline at Week 12	-0.567 (± 0.7875)	-0.42 (± 0.8767)		

Notes:

[10] - Number of subjects analyzed is the number of subjects included in the MMRM analyses.

[11] - Number of subjects analyzed is the number of subjects included in the MMRM analyses.

Statistical analyses

Statistical analysis title	Treatment comparisons of CFB in total asthma score
Comparison groups	Benralizumab 30 mg Q4W v Placebo

Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.266 [12]
Method	Mixed models analysis
Parameter estimate	Difference of Least Square Means
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.1

Notes:

[12] - Hypothesis testing were reported using 2-sided 5% level tests with nominal p-values (i.e., not adjusted for multiplicity).

Secondary: Change from baseline in total asthma rescue medication use (puffs) at Week 12

End point title	Change from baseline in total asthma rescue medication use (puffs) at Week 12

End point description:

The number of rescue medication inhalations and nebulizer treatments taken were recorded by the patient in the asthma daily diary twice daily. The number of inhalations (puffs) per day was calculated as [number of night inhaler puffs] + 2 x [number of night nebulizer times] + number of day inhaler puffs + 2 x [number of day nebulizer times]. The outcome variable for total asthma rescue medication use (puffs) was change from baseline at Week 12 in weekly total asthma rescue medication use (puffs). The changes are compared between benralizumab 30 mg Q4W and placebo by using the mixed-effect model repeated measures (MMRM) with baseline blood eosinophil count (≥300 cells/µL or <300 cells/µL), protocol specified visit, region (Europe or North America) and treatment*visit interaction as fixed effects and baseline total asthma rescue medication use (puffs) as a covariate.

End point type	Secondary

End point timeframe:

Up to Week 12

End point values	Benralizumab 30 mg Q4W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105[13]	105[14]		
Units: Puffs				
arithmetic mean (standard deviation)				
Baseline	2.953 (± 3.0794)	2.641 (± 3.0671)		
Week 12	1.647 (± 2.4782)	2.07 (± 2.6848)		
Change from baseline at Week 12	-1.098 (± 2.3588)	-0.665 (± 2.2744)		

Notes:

[13] - Number of subjects analyzed is the number of subjects included in the MMRM analyses.

[14] - Number of subjects analyzed is the number of subjects included in the MMRM analyses.

Statistical analyses

Statistical analysis title	Treatment comparisons of CFB in total resc med use
Comparison groups	Benralizumab 30 mg Q4W v Placebo
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2 [15]
Method	Mixed models analysis
Parameter estimate	Difference of Least Square Means
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	0.19

Notes:

[15] - Hypothesis testing were reported using 2-sided 5% level tests with nominal p-values (i.e., not adjusted for multiplicity).

Secondary: Change from baseline in proportion of nights with nocturnal awakenings at Week 12

End point title	Change from baseline in proportion of nights with nocturnal awakenings at Week 12

End point description:

Nocturnal awakenings due to asthma symptoms and requiring rescue medication use was recorded by the patient in the asthma daily diary each morning. Proportion of nights with nocturnal awakenings was defined as the number of nights with awakenings due to asthma and requiring rescue medication divided by number of nights with data for awakening due to asthma. The outcome variable for proportion of nights with nocturnal awakenings was change from baseline at Week 12 in weekly proportion of nights with nocturnal awakenings. The changes are compared between benralizumab 30 mg Q4W and placebo by using the mixed-effect model repeated measures (MMRM) with baseline blood eosinophil count (≥300 cells/µL or <300 cells/µL), protocol specified visit, region (Europe or North America) and treatment*visit interaction as fixed effects and baseline proportion of nights with nocturnal awakenings as a covariate.

End point type	Secondary

End point timeframe:

Up to Week 12

End point values	Benralizumab 30 mg Q4W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105[16]	105[17]		
Units: Proportion				
arithmetic mean (standard deviation)				
Baseline	0.246 (± 0.2924)	0.279 (± 0.3326)		
Week 12	0.086 (± 0.2003)	0.144 (± 0.2796)		
Change from baseline at Week 12	-0.158 (± 0.2515)	-0.139 (± 0.2659)		

Notes:

[16] - Number of subjects analyzed is the number of subjects included in the MMRM analyses.

[17] - Number of subjects analyzed is the number of subjects included in the MMRM analyses.

Statistical analyses

Statistical analysis title	Treatment comparisons of CFB in prop of noct awak
Comparison groups	Benralizumab 30 mg Q4W v Placebo
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38 [18]
Method	Mixed models analysis
Parameter estimate	Difference of Least Square Means
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.03

Notes:

[18] - Hypothesis testing were reported using 2-sided 5% level tests with nominal p-values (i.e., not adjusted for multiplicity).

Secondary: Change from baseline in mean ACQ-6 score at Week 12

End point title	Change from baseline in mean ACQ-6 score at Week 12

End point description:

The asthma control questionnaire, ACQ-6, consists of six questions; all assessed on a 7-point scale from 0 to 6, where 0 represents good control and 6 represents poor control. The overall score is the mean of the responses to each of the six questions. The outcome variable for ACQ-6 score was change from baseline at Week 12. The changes are compared between benralizumab 30 mg Q4W and placebo by using the mixed-effect repeated measures (MMRM) with baseline blood eosinophil count (≥300 cells/µL or <300 cells/µL), protocol specified visit (Week 4, Week 8, Week 12), region (Europe or North America) and treatment*visit interaction as fixed effects and baseline ACQ-6 score as a covariate.

End point type	Secondary

End point timeframe:

Up to Week 12

End point values	Benralizumab 30 mg Q4W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104[19]	104[20]		
Units: Point scale				
arithmetic mean (standard deviation)				
Baseline	2.119 (± 0.8423)	2.092 (± 0.8975)		
Week 12	1.428 (± 0.8621)	1.568 (± 1.009)		
Change from baseline at Week 12	-0.714 (± 0.87)	-0.495 (± 0.7908)		

Notes:

[19] - Number of subjects analyzed is the number of subjects included in the MMRM analyses.

[20] - Number of subjects analyzed is the number of subjects included in the MMRM analyses.

Statistical analyses

Statistical analysis title	Treatment comparisons of CFB in ACQ-6 score
Comparison groups	Benralizumab 30 mg Q4W v Placebo

Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.114 [21]
Method	Mixed models analysis
Parameter estimate	Difference of Least Square Means
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	0.04

Notes:

[21] - Hypothesis testing were reported using 2-sided 5% level tests with nominal p-values (i.e., not adjusted for multiplicity).

Secondary: Asthma exacerbations

End point title	Asthma exacerbations

End point description:

An asthma exacerbation was defined as a worsening of asthma that led to use of systemic corticosteroids for at least 3 days (a single depo-injectable dose of corticosteroids was considered equivalent to a 3-day course of systemic corticosteroids) or an emergency room or urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or urgent care center) due to asthma that required systemic corticosteroids (as per above) or 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. Number of patients experiencing an event included in the definition of asthma exacerbation was presented.

End point type	Secondary

End point timeframe:

Up to Week 12

End point values	Benralizumab 30 mg Q4W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	105		
Units: Patients per number of exacerbations				
= 0	105	103		
= 1	0	2		
= 2	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in AQLQ(S)+12 total and domain scores at Week 12

End point title	Change from baseline in AQLQ(S)+12 total and domain scores at Week 12

End point description:

The asthma quality of life questionnaire for 12 years and older, AQLQ(S)+12, consists of 32 questions; all assessed on a 7-point scale from 7 to 1, where 7 represents no impairment and 1 represents severe impairment. The 4 individual domain scores (symptoms, activity limitations, emotional function, and environmental stimuli) are the means of the responses to the questions in each of the domains. The overall score is calculated as the mean response to all questions. The outcome variable for AQLQ(S)+12 score was change from baseline at Week 12. The changes are compared between benralizumab 30 mg Q4W and placebo by using the analyse of covariance (ANCOVA) with baseline blood eosinophil count (≥300 cells/µL or <300 cells/µL) and region (Europe or North America) as fixed effects and baseline AQLQ(S)+12 score as a covariate.

End point type	Secondary

End point timeframe:

Up to Week 12

End point values	Benralizumab 30 mg Q4W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102[22]	102[23]		
Units: Point scale				
arithmetic mean (standard deviation)				
Total score - Baseline	4.825 (± 0.9787)	4.895 (± 1.0339)		
Total score - W12	5.415 (± 0.9478)	5.284 (± 1.0851)		
Total score - CFB at W12	0.585 (± 0.8675)	0.357 (± 0.7979)		
Symptoms score - Baseline	4.649 (± 1.0367)	4.692 (± 1.083)		
Symptoms score - W12	5.38 (± 1.0076)	5.212 (± 1.1373)		
Symptoms score - CFB at W12	0.727 (± 0.989)	0.483 (± 0.9243)		
Activity limitations score - Baseline	5.017 (± 1.0029)	5.048 (± 1.0277)		
Activity limitations score - W12	5.503 (± 0.9672)	5.343 (± 1.0803)		
Activity limitations score - CFB at W12	0.481 (± 0.8156)	0.275 (± 0.8105)		
Emotional function score - Baseline	4.95 (± 1.277)	5.04 (± 1.373)		
Emotional function score - W12	5.54 (± 1.215)	5.45 (± 1.307)		
Emotional function score - CFB at W12	0.57 (± 1.094)	0.35 (± 1.014)		
Environmental stimuli score - Baseline	4.658 (± 1.332)	4.905 (± 1.3554)		
Environmental stimuli score - W12	5.12 (± 1.291)	5.13 (± 1.3372)		
Environmental stimuli score - CFB at W12	0.466 (± 1.0135)	0.216 (± 0.9505)		

Notes:

[22] - Number of subjects analyzed is the number of subjects included in the ANCOVA analyses.

[23] - Number of subjects analyzed is the number of subjects included in the ANCOVA analyses.

Statistical analyses

Statistical analysis title	Treatment comparisons of CFB in total score

Statistical analysis description:

Parameter: Total score

Comparison groups	Benralizumab 30 mg Q4W v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.055 [24]
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.42

Notes:

[24] - Hypothesis testing were reported using 2-sided 5% level tests with nominal p-values (i.e., not adjusted for multiplicity).

Statistical analysis title	Treatment comparisons of CFB in symptoms score
Statistical analysis description:	
Parameter: Symptoms score	
Comparison groups	Benralizumab 30 mg Q4W v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.063 [25]
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.47

Notes:

[25] - Hypothesis testing were reported using 2-sided 5% level tests with nominal p-values (i.e., not adjusted for multiplicity).

Statistical analysis title	Treatment comparisons of CFB in act. limit. score
Statistical analysis description:	
Parameter: Activity limitation score	
Comparison groups	Benralizumab 30 mg Q4W v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.061 [26]
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.41

Notes:

[26] - Hypothesis testing were reported using 2-sided 5% level tests with nominal p-values (i.e., not adjusted for multiplicity).

Statistical analysis title	Treatment comparisons of CFB in emot. funct. score

Statistical analysis description:

Parameter: Emotional function score

Comparison groups	Benralizumab 30 mg Q4W v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.156 [27]
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.45

Notes:

[27] - Hypothesis testing were reported using 2-sided 5% level tests with nominal p-values (i.e., not adjusted for multiplicity).

Statistical analysis title	Treatment comparisons of CFB in envir. stim. score

Statistical analysis description:

Parameter: Environmental stimuli score

Comparison groups	Benralizumab 30 mg Q4W v Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.135 [28]
Method	ANCOVA
Parameter estimate	Difference of Least Square Means
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.44

Notes:

[28] - Hypothesis testing were reported using 2-sided 5% level tests with nominal p-values (i.e., not adjusted for multiplicity).

Secondary: Serum Concentrations (ng/mL)

End point title	Serum Concentrations (ng/mL)

End point description:

Blood samples (processed to serum) for pharmacokinetic assessments were collected from all patients at

baseline prior to first benralizumab administration at Day 1, at the Week 12 visit or the IP discontinuation visit, and at the Week 20 follow-up visit. Serum concentrations of benralizumab were determined using a validated electrochemiluminescent (ECL) immunoassay.

End point type	Secondary

End point timeframe:

Up to week 20

End point values	Benralizumab 30 mg Q4W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	0[29]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Week 12	999.16 (± 95.53)	()		
Week 20	59.04 (± 317.71)	()		

Notes:

[29] - All Placebo patients had concentration below the limit of quantification (3.86 ng/mL).

Statistical analyses

No statistical analyses for this end point

Secondary: Peripheral blood eosinophil levels

End point title	Peripheral blood eosinophil levels

End point description:

Peripheral blood eosinophil levels assessments were collected from all patients at baseline prior to first benralizumab administration at Day 1, at the Week 12 visit or the IP discontinuation visit, and at the Week 20 follow-up visit.

End point type	Secondary

End point timeframe:

Up to Week 20

End point values	Benralizumab 30 mg Q4W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	105		
Units: Cells/µL				
median (full range (min-max))				
Baseline	170 (30 to 1060)	220 (40 to 1140)		
Week 12	0 (0 to 110)	230 (30 to 1000)		
Change from baseline at Week 12	-170 (-1060 to 40)	10 (-710 to 910)		
Week 20	0 (0 to 490)	210 (40 to 1440)		

Change from Baseline at Week 20	-160 (-1060 to 130)	10 (-400 to 910)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs, including SAEs, in the on-study period were defined as those with onset between day of the first dose of study treatment and last scheduled follow-up visit, inclusive.

Adverse event reporting additional description:

The safety analysis set comprised all patients who received at least one dose of IP. Patients were classified according to the treatment they actually received. A patient who has on one or several occasions received active treatment was classified as active.
No subject received wrong dose in the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo administered subcutaneously every 4 weeks

Reporting group title	Benralizumab 30 mg Q4W

Reporting group description:

Benralizumab administered subcutaneously every 4 weeks

Serious adverse events	Placebo	Benralizumab 30 mg Q4W	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 105 (1.90%)	2 / 106 (1.89%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma			
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Pancytopenia			

subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Benralizumab 30 mg Q4W	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 105 (13.33%)	19 / 106 (17.92%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 105 (0.95%)	4 / 106 (3.77%)	
occurrences (all)	1	7	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 105 (2.86%)	4 / 106 (3.77%)	
occurrences (all)	3	4	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 105 (7.62%)	8 / 106 (7.55%)	
occurrences (all)	9	8	
Upper respiratory tract infection			
subjects affected / exposed	5 / 105 (4.76%)	5 / 106 (4.72%)	
occurrences (all)	5	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported