



Clinical trial results:

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid plus Long-acting 2 Agonist and Chronic Oral Corticosteroid Therapy (ZONDA)

Summary

EudraCT number	2013-002523-42
Trial protocol	DE PL ES BG
Global end of trial date	29 September 2016

Results information

Result version number	v1 (current)
This version publication date	09 August 2017
First version publication date	09 August 2017

Trial information

Trial identification

Sponsor protocol code	D3250C00020
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Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	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	29 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 September 2016
Global end of trial reached?	Yes
Global end of trial date	29 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of 2 dosing regimens of benralizumab on percentage reduction of oral corticosteroid (OCS) dose in adult patients with uncontrolled asthma.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 April 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects**Subjects enrolled per country**

Country: Number of subjects enrolled	Argentina: 10
Country: Number of subjects enrolled	Bulgaria: 8
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	Chile: 9
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 45
Country: Number of subjects enrolled	Poland: 45
Country: Number of subjects enrolled	Korea, Republic of: 11
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Turkey: 11
Country: Number of subjects enrolled	Ukraine: 28
Country: Number of subjects enrolled	United States: 17
Worldwide total number of subjects	220
EEA total number of subjects	111

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)	192
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

369 participants signed informed consent. 271 entered run in/OCS optimization period. 220 participants were randomized to receive treatment with benralizumab 30 mg Q4W, Q8W, or placebo. Of the 220 patients randomised, all (100.0%) received treatment with study drug.

Period 1

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

Arms

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

Arm description:

Benralizumab administered subcutaneously every 4 weeks

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

Dosage and administration details:

30 mg

Arm title	Benralizumab 30 mg q.8 weeks
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Arm description:

Benralizumab administered subcutaneously every 4 weeks for the first 3 doses and then every 8 weeks

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

Dosage and administration details:

30 mg

Arm title	Placebo
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Arm description:

Placebo administered subcutaneously

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

Number of subjects in period 1	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo
Started	72	73	75
Completed	68	69	72
Not completed	4	4	3
Adverse event, serious fatal	-	2	-
Consent withdrawn by subject	4	1	-
Adverse event, non-fatal	-	-	1
Study specific withdrawal criteria	-	1	1
Lost to follow-up	-	-	1

Baseline characteristics

Reporting groups

Reporting group title	Benralizumab 30 mg q.4 weeks
Reporting group description: Benralizumab administered subcutaneously every 4 weeks	
Reporting group title	Benralizumab 30 mg q.8 weeks
Reporting group description: Benralizumab administered subcutaneously every 4 weeks for the first 3 doses and then every 8 weeks	
Reporting group title	Placebo
Reporting group description: Placebo administered subcutaneously	

Reporting group values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo
Number of subjects	72	73	75
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)	64	61	67
From 65-84 years	8	12	8
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	50.2	52.9	49.9
standard deviation	± 12	± 10.1	± 11.7
Gender, Male/Female Units: Subjects			
Female	40	47	48
Male	32	26	27

Reporting group values	Total		
Number of subjects	220		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	192		

From 65-84 years	28		
85 years and over	0		

Age Continuous Units: Years arithmetic mean standard deviation	-		
Gender, Male/Female Units: Subjects			
Female	135		
Male	85		

End points

End points reporting groups

Reporting group title	Benralizumab 30 mg q.4 weeks
Reporting group description: Benralizumab administered subcutaneously every 4 weeks	
Reporting group title	Benralizumab 30 mg q.8 weeks
Reporting group description: Benralizumab administered subcutaneously every 4 weeks for the first 3 doses and then every 8 weeks	
Reporting group title	Placebo
Reporting group description: Placebo administered subcutaneously	

Primary: Percentage reduction in final OCS dose compared with baseline while maintaining asthma control

End point title	Percentage reduction in final OCS dose compared with baseline while maintaining asthma control
End point description: Baseline OCS dose is the dose upon which the patient is stabilised at randomisation (Week 0). Final OCS dose is the dose at Week 28. The percentage reduction from baseline is defined as: $\{(\text{Baseline dose} - \text{final dose}) / \text{baseline dose}\} * 100\%$. If a patient discontinues from the study during a given dose reduction period, or the patient experiences an exacerbation between Weeks 24 and 28 or immediately before discontinuation, then the final OCS dose will be 1 dose level higher than that which directly preceded the event.	
End point type	Primary
End point timeframe: Week 28	

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	73	75	
Units: Percent				
median (confidence interval 95%)	75 (50 to 83.3)	75 (60 to 87.5)	25 (0 to 33.3)	

Statistical analyses

Statistical analysis title	Wilcoxon rank-sum test
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	33.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.7
upper limit	50

Statistical analysis title	Wilcoxon rank-sum test
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	37.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.8
upper limit	50

Secondary: Percentage reduction in final OCS dose compared with baseline while maintaining asthma control for patients with baseline eosinophils $\geq 300/\mu\text{L}$

End point title	Percentage reduction in final OCS dose compared with baseline while maintaining asthma control for patients with baseline eosinophils $\geq 300/\mu\text{L}$
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End point description:

Baseline OCS dose is the dose upon which the patient is stabilised at randomisation (Week 0). Final OCS dose is the dose at Week 28. The percentage reduction from baseline is defined as: $\{(\text{Baseline dose} - \text{final dose}) / \text{baseline dose}\} \times 100\%$. If a patient discontinues from the study during a given dose reduction period, or the patient experiences an exacerbation between Weeks 24 and 28 or immediately before discontinuation, then the final OCS dose will be 1 dose level higher than that which directly preceded the event.

End point type	Secondary
End point timeframe:	
Week 28	

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	61	64	
Units: Percent				
median (confidence interval 95%)	75 (60 to 100)	75 (60 to 91.7)	0 (0 to 28.6)	

Statistical analyses

Statistical analysis title	Wilcoxon rank-sum test
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	50
Confidence interval	
level	95 %
sides	2-sided
lower limit	25
upper limit	66.7

Statistical analysis title	Wilcoxon rank-sum test
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	50
Confidence interval	
level	95 %
sides	2-sided
lower limit	25
upper limit	66.7

Secondary: The proportion of patients with $\geq 50\%$ reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control

End point title	The proportion of patients with $\geq 50\%$ reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
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End point description:

Baseline OCS dose is the dose upon which the patient is stabilised at randomisation (Week 0). Final OCS dose is the dose at Week 28. The percentage reduction from baseline is defined as: $\{(\text{Baseline dose} - \text{final dose}) / \text{baseline dose}\} * 100\%$. If a patient discontinues from the study during a given dose reduction period, or the patient experiences an exacerbation between Weeks 24 and 28 or immediately before discontinuation, then the final OCS dose will be 1 dose level higher than that which directly preceded the event.

End point type	Secondary
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End point timeframe:

Week 28

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	73	75	
Units: Participants	48	48	28	

Statistical analyses

Statistical analysis title	CMH test
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.79
upper limit	7.22

Notes:

[1] - Controlling for region

Statistical analysis title	CMH test
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.57
upper limit	5.86

Notes:

[2] - Controlling for region

Secondary: The proportion of eligible patients with $\geq 100\%$ reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control

End point title	The proportion of eligible patients with $\geq 100\%$ reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
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End point description:

Baseline OCS dose is the dose upon which the patient is stabilised at randomisation (Week 0). Final OCS dose is the dose at Week 28. The percentage reduction from baseline is defined as: $\{(\text{Baseline dose} - \text{final dose}) / \text{baseline dose}\} * 100\%$. If a patient discontinues from the study during a given dose reduction period, or the patient experiences an exacerbation between Weeks 24 and 28 or immediately before discontinuation, then the final OCS dose will be 1 dose level higher than that which directly preceded the event.

End point type	Secondary
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End point timeframe:

Week 28

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39 ^[3]	42 ^[4]	42 ^[5]	
Units: Participants	22	22	8	

Notes:

[3] - Only eligible (ie, baseline OCS dose ≤ 12.5 mg) included.

[4] - Only eligible (ie, baseline OCS dose ≤ 12.5 mg) included.

[5] - Only eligible (ie, baseline OCS dose ≤ 12.5 mg) included.

Statistical analyses

Statistical analysis title	CMH test
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.002
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	4.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.58
upper limit	11.12

Notes:

[6] - Controlling for region

Statistical analysis title	CMH test
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	5.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.92
upper limit	14.21

Notes:

[7] - Controlling for region

Secondary: The proportion of patients with ≤ 5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control.

End point title	The proportion of patients with ≤ 5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control.
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End point description:

Baseline OCS dose is the dose upon which the patient is stabilised at randomisation (Week 0). Final OCS dose is the dose at Week 28. If a patient discontinues from the study during a given dose reduction period, or the patient experiences an exacerbation between Weeks 24 and 28 or immediately before discontinuation, then the final OCS dose will be 1 dose level higher than that which directly preceded the event.

End point type	Secondary
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End point timeframe:

Week 28

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	73	75	
Units: Participants	22	25	38	

Statistical analyses

Statistical analysis title	CMH test
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	= 0.012
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	0.83

Notes:

[8] - Controlling for region

Statistical analysis title	CMH test
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.053
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	1.01

Notes:

[9] - Controlling for region

Secondary: The proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control

End point title	The proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control
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End point description:

Final OCS dose is the dose at Week 28. If a patient discontinues from the study during a given dose reduction period, or the patient experiences an exacerbation between Weeks 24 and 28 or immediately before discontinuation, then the final OCS dose will be 1 dose level higher than that which directly preceded the event.

End point type	Secondary
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End point timeframe:

Week 28

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	73	75	
Units: Participants	44	43	25	

Statistical analyses

Statistical analysis title	CMH test
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	= 0.002
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.41
upper limit	5.31

Notes:

[10] - Controlling for region

Statistical analysis title	CMH test
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.6
upper limit	6.23

Notes:

[11] - Controlling for region

Secondary: Proportion of patients with ≥ 1 asthma exacerbation

End point title	Proportion of patients with ≥ 1 asthma exacerbation
End point description:	
Number and percentage of patients with at least one post randomization asthma exacerbation.	
End point type	Secondary

End point timeframe:

Immediately following the randomisation through Study Week 28

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	73	75	
Units: Participants	19	17	39	

Statistical analyses

Statistical analysis title	CMH test
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority ^[12]
P-value	= 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.65

Notes:

[12] - Controlling for region

Statistical analysis title	CMH test
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority ^[13]
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	0.56

Notes:

[13] - Controlling for region

Secondary: Time to the first asthma exacerbation

End point title	Time to the first asthma exacerbation
End point description:	
Time to the first occurrence of asthma exacerbation post randomisation	
End point type	Secondary
End point timeframe:	
The time from randomisation to the date of first asthma exacerbation	

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72 ^[14]	73 ^[15]	75 ^[16]	
Units: Participants				
Number of patients with exacerbations	19	37	39	

Notes:

[14] - median survival time is not estimable due to number of exacerbations had not reached 50%.

[15] - median survival time is not estimable due to number of exacerbations had not reached 50%.

[16] - median survival time = 155 days, however upper 95% CI for median is not estimable.

Statistical analyses

Statistical analysis title	Cox regression
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority ^[17]
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.66

Notes:

[17] - Covariates of treatment group, region, and number of exacerbations in the previous year.

Statistical analysis title	Cox regression
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority ^[18]
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.32

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.57

Notes:

[18] - Covariates of treatment group, region, and number of exacerbations in the previous year.

Secondary: Time to the first asthma exacerbation requiring hospitalization or ER visit

End point title	Time to the first asthma exacerbation requiring hospitalization or ER visit
End point description:	
Time to the first exacerbation requiring hospitalization or ER visit post randomisation	
End point type	Secondary
End point timeframe:	
The time from randomisation to the date of first asthma exacerbation	

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72 ^[19]	73 ^[20]	75 ^[21]	
Units: Participants				
# of pt. with exacerbations equiring HOSP/ER	4	1	9	

Notes:

[19] - No est. median survival time, # of exacerbations resulting hospitalization/ER had not reached 50%.

[20] - No est. median survival time, # of exacerbations resulting hospitalization/ER had not reached 50%.

[21] - No est. median survival time, # of exacerbations resulting hospitalization/ER had not reached 50%.

Statistical analyses

Statistical analysis title	Cox regression
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority ^[22]
P-value	= 0.042
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.63

Notes:

[22] - Covariates of treatment group, region, and any exacerbations in the previous year requiring hospitalization or ER.

Statistical analysis title	Cox regression
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority ^[23]
P-value	= 0.291
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	1.64

Notes:

[23] - Covariates of treatment group, region, and any exacerbations in the previous year requiring hospitalization or ER.

Secondary: Annual rate of asthma exacerbations

End point title	Annual rate of asthma exacerbations
End point description:	The annual asthma exacerbation rate is based on unadjudicated asthma exacerbations reported by the investigator.
End point type	Secondary
End point timeframe:	The time from randomisation to the date of week 28 visit (end of treatment) or last contact if the patient is lost to follow up

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	73	75	
Units: events/year				
least squares mean (confidence interval 95%)	0.83 (0.55 to 1.26)	0.54 (0.34 to 0.88)	1.83 (1.33 to 2.5)	

Statistical analyses

Statistical analysis title	Negative binomial (generalized linear model)
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo

Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority ^[24]
P-value	< 0.001
Method	negative binomial model
Parameter estimate	Rate ratio
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.53

Notes:

[24] - Covariates of treatment group, region, number of exacerbations in the previous year

Statistical analysis title	Negative binomial (generalized linear model)
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority ^[25]
P-value	= 0.003
Method	negative binomial model
Parameter estimate	Rate ratio
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	0.76

Notes:

[25] - Covariates of treatment group, region, number of exacerbations in the previous year

Secondary: Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization

End point title	Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization
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End point description:

The annual exacerbation rate associated with hospitalization or ER is based on unadjudicated annual exacerbations reported by the investigator.

End point type	Secondary
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End point timeframe:

The time from randomisation to the date of week 28 visit (end of treatment) or last contact if the patient is lost to follow up

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	73	75	
Units: events/year				
least squares mean (confidence interval 95%)	0.14 (0.05 to 0.38)	0.02 (0 to 0.18)	0.32 (0.16 to 0.65)	

Statistical analyses

Statistical analysis title	Negative binomial (generalized linear model)
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority ^[26]
P-value	= 0.018
Method	negative binomial model
Parameter estimate	Rate ratio
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.63

Notes:

[26] - Covariates of treatment group, region, any exacerbation requiring hospitalization/ER in the previous year

Statistical analysis title	Negative binomial (generalized linear model)
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority ^[27]
P-value	= 0.187
Method	negative binomial model
Parameter estimate	Rate ratio
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	1.49

Notes:

[27] - Covariates of treatment group, region, any exacerbation requiring hospitalization/ER in the previous year

Secondary: Number of days in hospital due to asthma

End point title	Number of days in hospital due to asthma
-----------------	--

End point description:

Number of days in hospital due to asthma, if none, 0 day is considered

End point type	Secondary
End point timeframe:	
The time from randomisation to the date of week 28 visit (end of treatment) or last contact if the patient is lost to follow up	

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	73	75	
Units: Days				
arithmetic mean (standard deviation)	0.3 (± 1.41)	0.5 (± 3.86)	1.2 (± 6.66)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 28 in pre-bronchodilator FEV1

End point title	Change from baseline to week 28 in pre-bronchodilator FEV1
End point description:	
Baseline is defined as the last non-missing value prior to the first dose of study treatment. Change from baseline to Week 28 in two treatment groups is compared to placebo group.	
End point type	Secondary
End point timeframe:	
From baseline to week 28, every four weeks	

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	68	73	
Units: Liter				
arithmetic mean (standard deviation)	0.23 (± 0.429)	0.255 (± 0.508)	0.114 (± 0.401)	

Statistical analyses

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

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority ^[28]
P-value	= 0.153
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.105
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.251

Notes:

[28] - Covariates of treatment group, region, baseline value, visit, and visit by treatment group interaction

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority ^[29]
P-value	= 0.129
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.112
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.033
upper limit	0.258

Notes:

[29] - Covariates of treatment group, region, baseline value, visit, and visit by treatment group interaction

Secondary: Change from baseline to week 28 in asthma symptom scores (Total)

End point title	Change from baseline to week 28 in asthma symptom scores (Total)
-----------------	--

End point description:

Asthma symptoms during night time and daytime are recorded by the patient in the asthma daily diary. Symptom score values are from 0 (No asthma symptom) to 3 (unable to sleep because of asthma, or unable to do normal activities due to asthma), and total asthma symptom score is the sum of the daytime and night time score (0 to 6). Lower score (0) is indicating better asthma symptom, while higher score (6) is indicating worse asthma symptom. Baseline is defined as the average of data collected from the evening of study day -14 to the morning of study day 1. Each time point is calculated as bi-weekly means based on daily diary data. If more than 50% of scores are missing in a 14 day period then this is considered as missing. Symptom score lower is better.

End point type	Secondary
----------------	-----------

End point timeframe:

From baseline to week 28, every two weeks

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	68	67	
Units: Scores on a scale				
arithmetic mean (standard deviation)	-0.58 (± 1.03)	-0.77 (± 1.03)	-0.58 (± 1.03)	

Statistical analyses

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority ^[30]
P-value	= 0.947
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.32

Notes:

[30] - Covariates of treatment group, region, baseline value, visit, and visit by treatment group interaction

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority ^[31]
P-value	= 0.291
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	0.16

Notes:

[31] - Covariates of treatment group, region, baseline value, visit, and visit by treatment group interaction

Secondary: Change from baseline to week 28 in asthma symptom scores (Daytime)

End point title	Change from baseline to week 28 in asthma symptom scores (Daytime)
-----------------	--

End point description:

Asthma symptoms during daytime are recorded by the patient in the asthma daily diary. Symptom score

values are from 0 (No asthma symptom) to 3 (unable to sleep because of asthma, or unable to do normal activities due to asthma). Lower score (0) is indicating better asthma symptom, while higher score (3) is indicating worse asthma symptom. Baseline is defined as the average of data collected from the evening of study day -14 to the morning of study day 1. Each time point is calculated as bi-weekly means based on daily diary data. If more than 50% of scores are missing in a 14 day period then this is considered as missing. Symptom score lower is better.

End point type	Secondary
----------------	-----------

End point timeframe:

From baseline to week 28, every two weeks

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	69	69	
Units: Scores on a scale				
arithmetic mean (standard deviation)	-0.32 (± 0.56)	-0.44 (± 0.52)	-0.32 (± 0.57)	

Statistical analyses

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority ^[32]
P-value	= 0.998
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.18

Notes:

[32] - Covariates of treatment group, region, baseline value, visit, and visit by treatment group interaction

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority ^[33]
P-value	= 0.177
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.05

Notes:

[33] - Covariates of treatment group, region, baseline value, visit, and visit by treatment group interaction

Secondary: Change from baseline to week 28 in asthma symptom scores (Nighttime)

End point title	Change from baseline to week 28 in asthma symptom scores (Nighttime)
-----------------	--

End point description:

Asthma symptoms during night time are recorded by the patient in the asthma daily diary. Symptom score values are from 0 (No asthma symptom) to 3 (unable to sleep because of asthma, or unable to do normal activities due to asthma). Lower score (0) is indicating better asthma symptom, while higher score (3) is indicating worse asthma symptom. Baseline is defined as the average of data collected from the evening of study day -14 to the morning of study day 1. Each time point is calculated as bi-weekly means based on daily diary data. If more than 50% of scores are missing in a 14 day period then this is considered as missing. Symptom score lower is better.

End point type	Secondary
----------------	-----------

End point timeframe:

From baseline to week 28, every two weeks

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	68	67	
Units: Scores on a scale				
arithmetic mean (standard deviation)	-0.27 (± 0.51)	-0.34 (± 0.54)	-0.27 (± 0.54)	

Statistical analyses

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority ^[34]
P-value	= 0.973
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.17

Notes:

[34] - Covariates of treatment group, region, baseline value, visit, and visit by treatment group interaction

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority ^[35]
P-value	= 0.48
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.11

Notes:

[35] - Covariates of treatment group, region, baseline value, visit, and visit by treatment group interaction

Secondary: Change from baseline to week 28 in rescue medication use

End point title	Change from baseline to week 28 in rescue medication use
End point description:	
Baseline is defined as the average of data collected from the evening of study day -14 to the morning of study day 1. Each timepoint is calculated as bi-weekly means based on daily diary data. If more than 50% of scores are missing in a 14 day period then this will be considered as missing. The number of inhalations (puffs) per day will be calculated as follows: Number of night inhaler puffs + 2 x [number of night nebulizer times] + number of day inhaler puffs + 2 x [number of day nebulizer times].	
End point type	Secondary
End point timeframe:	
From baseline to week 28, every two weeks	

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	68	67	
Units: number of puffs per day				
arithmetic mean (standard deviation)	-1.39 (± 2.86)	-2.58 (± 4.36)	-1.07 (± 2.86)	

Statistical analyses

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

Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority ^[36]
P-value	= 0.006
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.42
upper limit	-0.41

Notes:

[36] - Covariates of treatment group, region, baseline total asthma rescue medication use, visit, and visit by treatment group interaction

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority ^[37]
P-value	= 0.397
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.44
upper limit	0.57

Notes:

[37] - Covariates of treatment group, region, baseline total asthma rescue medication use, visit, and visit by treatment group interaction

Secondary: Change from baseline to week 28 in home lung function (morning peak expiratory flow)

End point title	Change from baseline to week 28 in home lung function (morning peak expiratory flow)
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End point description:

Morning peak expiratory flow change from baseline to week 28. Baseline is defined as the average of data collected from the evening of study day -14 to the morning of study day 1. Each timepoint is calculated as bi-weekly means based on daily diary data

End point type	Secondary
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End point timeframe:

From baseline to week 28, every two weeks

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	68	67	
Units: Liter/min				
arithmetic mean (standard deviation)	32.697 (\pm 89.457)	43.022 (\pm 73.303)	10.884 (\pm 69.356)	

Statistical analyses

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority ^[38]
P-value	= 0.143
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	19.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.58
upper limit	45.07

Notes:

[38] - Covariates of treatment group, region, baseline value, visit, and visit by treatment group interaction

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority ^[39]
P-value	= 0.023
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	30.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.26
upper limit	55.76

Notes:

[39] - Covariates of treatment group, region, baseline value, visit, and visit by treatment group interaction

Secondary: Change from baseline to week 28 in home lung function (evening peak expiratory flow)

End point title	Change from baseline to week 28 in home lung function (evening peak expiratory flow)
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End point description:

Evening peak expiratory flow change from baseline to week 28. Baseline is defined as the average of data collected from the evening of study day -14 to the morning of study day 1. Each timepoint is calculated as bi-weekly means based on daily diary data

End point type	Secondary
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End point timeframe:

From baseline to week 28, every two weeks

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	69	66	
Units: Liter/min				
arithmetic mean (standard deviation)	21.885 (\pm 83.136)	34.157 (\pm 69.287)	2.933 (\pm 72.302)	

Statistical analyses

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority ^[40]
P-value	= 0.237
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	15.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.08
upper limit	40.46

Notes:

[40] - Covariates of treatment group, region, baseline value, visit, and visit by treatment group interaction

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority ^[41]
P-value	= 0.014
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	31.52

Confidence interval	
level	95 %
sides	2-sided
lower limit	6.32
upper limit	56.71

Notes:

[41] - Covariates of treatment group, region, baseline value, visit, and visit by treatment group interaction

Secondary: Change from baseline to week 28 in the proportion of nights with awakening due to asthma requiring rescue medication

End point title	Change from baseline to week 28 in the proportion of nights with awakening due to asthma requiring rescue medication
-----------------	--

End point description:

Baseline is defined as the proportion of nights from the evening of study day -14 to the morning of study day 1. Each timepoint is calculated as bi-weekly proportions based on daily diary data. If more than 50% of data are missing in a 14 day period then this will be considered as missing. Proportion of nights with nocturnal awakenings is defined as the number of nights with awakenings due to asthma and requiring rescue medication divided by number of nights with data.

End point type	Secondary
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End point timeframe:

From baseline to week 28, measure each two weeks

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	68	67	
Units: Proportion				
arithmetic mean (standard deviation)	-0.158 (± 0.283)	-0.2 (± 0.337)	-0.186 (± 0.344)	

Statistical analyses

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority ^[42]
P-value	= 0.742
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.11

Notes:

[42] - Covariates of treatment group, region, baseline proportion of nights with nocturnal awakening, visit, and visit by treatment group interaction

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority ^[43]
P-value	= 0.693
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.07

Notes:

[43] - Covariates of treatment group, region, baseline proportion of nights with nocturnal awakening, visit, and visit by treatment group interaction

Secondary: Change from baseline to week 28 in ACQ-6

End point title	Change from baseline to week 28 in ACQ-6
End point description:	
ACQ-6 contains one bronchodilator question and 5 symptom questions. Questions are rated from 0 (totally controlled) to 6 (severely uncontrolled). Mean ACQ-6 score is the average of the responses. Mean scores of ≤ 0.75 indicates well-controlled asthma, scores between 0.75 to ≤ 1.5 indicate partly controlled asthma, and > 1.5 indicates not well controlled asthma.	
End point type	Secondary
End point timeframe:	
From baseline to week 28, every two weeks	

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	66	66	67	
Units: Scores on a scale				
arithmetic mean (standard deviation)	-0.86 (\pm 0.95)	-1.09 (\pm 1.09)	-0.68 (\pm 1.1)	

Statistical analyses

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

Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority ^[44]
P-value	= 0.139
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.55
upper limit	0.08

Notes:

[44] - Covariates of treatment group, region, baseline value, visit, and visit by treatment group interaction

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority ^[45]
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.86
upper limit	-0.23

Notes:

[45] - Covariates of treatment group, region, baseline value, visit, and visit by treatment group interaction

Secondary: ACQ-6 responders (improvement) at Week 28

End point title	ACQ-6 responders (improvement) at Week 28
End point description:	
Improvement is defined as ACQ-6 (End of treatment - baseline) ≤ -0.5 . No change is defined as ACQ-6 (End of treatment - baseline) > -0.5 and < 0.5 . Deterioration is defined as ACQ-6 (End of treatment - baseline) ≥ 0.5 . ACQ-6 score is defined as the average of the first 6 items of the ACQ questionnaire on symptoms, activity limitations and rescue medication. Scores range from 0 (totally controlled) to 6 (severely uncontrolled). Baseline is defined as the last non-missing value prior to randomisation. End of treatment is defined as week 28. Patients with missing or non-evaluable ACQ-6 at week 28 are considered non-responder.	
End point type	Secondary
End point timeframe:	
Week 28	

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	73	75	
Units: Participants	41	46	41	

Statistical analyses

Statistical analysis title	Logistic regression
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority ^[46]
P-value	= 0.155
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.661
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.826
upper limit	3.34

Notes:

[46] - Covariates of treatment group, region, baseline value, and number of exacerbations in the previous year

Statistical analysis title	Logistics regression
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority ^[47]
P-value	= 0.658
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.165
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.592
upper limit	2.295

Notes:

[47] - Covariates of treatment group, region, baseline value, and number of exacerbations in the previous year

Secondary: Change from baseline to week 28 in AQLQ(S)+12 (Overall)

End point title	Change from baseline to week 28 in AQLQ(S)+12 (Overall)
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End point description:

AQLQ(S)+12 overall score is defined as the average of all 32 questions in the AQLQ(S)+12 questionnaire. AQLQ(S)+12 is a 7-point scale questionnaire, ranging from 7 (no impairment) to 1 (severe impairment). Total or domain score change of ≥ 0.5 are considered clinically meaningful.

End point type	Secondary
End point timeframe:	
From baseline to week 28, every four weeks	

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	66	67	68	
Units: Scores on a scale				
arithmetic mean (standard deviation)	0.9 (± 0.93)	1.05 (± 1.04)	0.67 (± 1.1)	

Statistical analyses

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority ^[48]
P-value	= 0.151
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.53

Notes:

[48] - Covariates of treatment group, region, baseline value, visit, and visit by treatment group interaction

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority ^[49]
P-value	= 0.004
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	0.76

Notes:

[49] - Covariates of treatment group, region, baseline value, visit, and visit by treatment group interaction

Secondary: AQLQ(s)+12 responders (improvement) at Week 28

End point title	AQLQ(s)+12 responders (improvement) at Week 28
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End point description:

AQLQ(S)+12 overall score is defined as the average of all 32 questions in the AQLQ(S)+12 questionnaire. Improvement is defined as AQLQ(S)+12 (End of treatment - baseline) ≥ 0.5 . No change is defined as AQLQ(S)+12 (End of treatment - baseline) > -0.5 and < 0.5 . Deterioration is defined as AQLQ(S)+12 (End of treatment - baseline) ≤ -0.5 . Baseline is defined as the last AQLQ(S)+12 score prior to randomisation. End of treatment is defined as week 28. Patients with missing or non-evaluable score at week 28 are considered as non-responder.

End point type	Secondary
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End point timeframe:

Week 28

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	73	75	
Units: Participants	43	44	39	

Statistical analyses

Statistical analysis title	Logistic regression
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority ^[50]
P-value	= 0.22
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.538
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.773
upper limit	3.06

Notes:

[50] - Covariates of treatment group, region, baseline value, and number of exacerbations in the previous year

Statistical analysis title	Logistic regression
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo

Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority ^[51]
P-value	= 0.108
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.783
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.882
upper limit	3.605

Notes:

[51] - Covariates of treatment group, region, baseline value, and number of exacerbations in the previous year

Secondary: Extent of Exposure

End point title	Extent of Exposure
End point description:	
Duration of exposure from first dose date to last dose date.	
End point type	Secondary
End point timeframe:	
From first dose to Week 24	

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	73	75	
Units: Days				
arithmetic mean (standard deviation)	162.53 (± 30.09)	159.77 (± 35.781)	167.05 (± 10.697)	

Statistical analyses

No statistical analyses for this end point

Secondary: Serum concentration of Benralizumab

End point title	Serum concentration of Benralizumab
End point description:	
Pre-dose serum concentrations at each visit	
End point type	Secondary
End point timeframe:	
Pre-first dose to Week 36	

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	71	72	0 ^[52]	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Baseline (n=69, 71)	0 (± 0)	0 (± 0)	()	
Week 4 (n=67, 71)	804.37 (± 52.77)	721.42 (± 52.3)	()	
week 8 (n=66, 69)	1152.96 (± 53.16)	1019.65 (± 89.51)	()	
Week 12 (n=68, 67)	1319.14 (± 66.05)	1057.91 (± 125.74)	()	
Week 16 (n=67, 67)	1337.98 (± 118.9)	303.54 (± 144.53)	()	
Week 24 (n=65, 66)	1162.62 (± 151.35)	185.17 (± 278.32)	()	
Week 28 (n=65, 65)	1125.96 (± 173.79)	684.57 (± 205.67)	()	
Week 36 (n=2, 4)	11.11 (± 2140.87)	5.92 (± 1230.68)	()	

Notes:

[52] - No active drug in placebo group, thus not in the PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-drug antibody response

End point title	Anti-drug antibody response
End point description:	
Number and percentage of patients in different ADA response categories	
End point type	Secondary
End point timeframe:	
From baseline to follow-up Week 36	

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	73	75	
Units: Participant				
Positive at any visit (n=72, 73, 75)	5	7	6	
Baseline and Post-baseline Positive (n=68, 69, 75)	0	0	3	
Only post-baseline positive (n=71, 70, 75)	5	6	3	
Only baseline positive (n=69, 72, 75)	0	1	0	
Persistently positive (n=71, 70, 75)	4	6	5	
Transient positive (n=71, 70, 75)	1	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in blood eosinophil counts

End point title	Percent change from baseline in blood eosinophil counts
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End point description:

Percent change from baseline in blood eosinophil counts at week 28

End point type	Secondary
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End point timeframe:

From baseline to Week 28

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63	62	66	
Units: percent				
arithmetic mean (standard deviation)	-97.4 (± 12.93)	-94.9 (± 16.54)	45.5 (± 239.51)	

Statistical analyses

Statistical analysis title	Mixed effect repeated measurement analysis
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Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
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Number of subjects included in analysis	128
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Analysis specification	Pre-specified
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Analysis type	superiority ^[53]
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P-value	< 0.001
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Method	Mixed models analysis
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Parameter estimate	Mean difference (final values)
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Point estimate	-159.4
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	-217.9
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upper limit	-100.9
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Notes:

[53] - Covariates of treatment group, region, baseline value, visit, and visit by treatment group interaction

Statistical analysis title	Mixed effect repeated measurement analysis
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority ^[54]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-162.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-220.1
upper limit	-104.3

Notes:

[54] - Covariates of treatment group, region, baseline value, visit, and visit by treatment group interaction

Secondary: Total Lung Capacity

End point title	Total Lung Capacity
End point description:	
Change from baseline in total lung capacity	
End point type	Secondary
End point timeframe:	
From baseline to Week 28	

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	26	23	
Units: Liter				
arithmetic mean (standard deviation)				
Week 12 (n=17, 23, 17)	-0.02 (± 0.95)	-0.07 (± 0.68)	-0.3 (± 1.08)	
Week 28 (n=14, 18, 15)	0.11 (± 1.31)	-0.21 (± 0.7)	-0.47 (± 1.47)	

Statistical analyses

No statistical analyses for this end point

Secondary: Residual Volume

End point title	Residual Volume
End point description:	
Change from baseline in residual volume	
End point type	Secondary
End point timeframe:	
From baseline to Week 28	

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	26	23	
Units: Liter				
arithmetic mean (standard deviation)				
Week 12 (n=17, 23, 17)	0.02 (± 1)	-0.22 (± 0.74)	-0.35 (± 1.03)	
Week 28 (n=14, 18, 15)	0.07 (± 1.34)	-0.31 (± 0.71)	-0.41 (± 1.27)	

Statistical analyses

No statistical analyses for this end point

Secondary: Vital Capacity

End point title	Vital Capacity
End point description:	
Change from baseline in vital capacity	
End point type	Secondary
End point timeframe:	
From baseline to Week 28	

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	26	23	
Units: Liter				
arithmetic mean (standard deviation)				
Week 12 (n=17, 24, 18)	0.15 (± 0.8)	0.18 (± 0.35)	0.13 (± 0.89)	
Week 28 (n=14, 18, 15)	0.15 (± 0.41)	0.11 (± 0.48)	-0.08 (± 0.41)	

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Residual Capacity

End point title	Functional Residual Capacity
End point description:	
Change from baseline in functional residual capacity	
End point type	Secondary

End point timeframe:
From baseline to Week 28

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	26	23	
Units: Liter				
arithmetic mean (standard deviation)				
Week 12 (n=17,23, 18)	-0.05 (± 1.06)	-0.09 (± 0.74)	-0.38 (± 0.99)	
Week 28 (n=13,18, 15)	-0.15 (± 1.49)	-0.26 (± 0.74)	-0.43 (± 1.25)	

Statistical analyses

No statistical analyses for this end point

Secondary: Inspiratory Capacity

End point title | Inspiratory Capacity

End point description:

Change from baseline in inspiratory capacity

End point type | Secondary

End point timeframe:

From baseline to Week 28

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	26	23	
Units: Liter				
arithmetic mean (standard deviation)				
Week 12 (n=17, 23, 17)	0.44 (± 1.22)	0.14 (± 0.88)	-0.01 (± 0.4)	
Week 28 (n=14, 17, 15)	0.52 (± 1.16)	0.09 (± 1.01)	-0.02 (± 0.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Categories of percent reduction from baseline in final OCS dose while maintaining asthma control

End point title | Categories of percent reduction from baseline in final OCS dose while maintaining asthma control

End point description:

Percent reduction from baseline in final OCS dose, separated by categories.

End point type	Secondary
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End point timeframe:

Week 28

End point values	Benralizumab 30 mg q.4 weeks	Benralizumab 30 mg q.8 weeks	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	73	75	
Units: Participant				
>=90% reduction	24	27	9	
>=75% reduction	38	37	15	
>=50% reduction	48	48	28	
>0% reduction	55	58	40	
No change or any increase	17	15	35	

Statistical analyses

Statistical analysis title	Proportional odds ratio model
Comparison groups	Benralizumab 30 mg q.8 weeks v Placebo
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority ^[55]
P-value	< 0.001
Method	Multinomial logit
Parameter estimate	Odds ratio (OR)
Point estimate	4.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.22
upper limit	7.63

Notes:

[55] - Covariates of treatment group, region, and baseline OCS dosage

Statistical analysis title	Proportional odds ratio model
Comparison groups	Benralizumab 30 mg q.4 weeks v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority ^[56]
P-value	< 0.001
Method	Multinomial logit
Parameter estimate	Odds ratio (OR)
Point estimate	4.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.22
upper limit	7.57

Notes:

[56] - Covariates of treatment group, region, and baseline OCS dosage

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall study period

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Benra 30 mg q.4 weeks
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Reporting group description:

Benralizumab administered subcutaneously every 4 weeks

Reporting group title	Placebo
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Reporting group description:

Placebo administered subcutaneously

Reporting group title	Benra 30 mg q.8 weeks
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Reporting group description:

Benralizumab administered subcutaneously every 8 weeks

Serious adverse events	Benra 30 mg q.4 weeks	Placebo	Benra 30 mg q.8 weeks
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 72 (9.72%)	14 / 75 (18.67%)	7 / 73 (9.59%)
number of deaths (all causes)	0	0	2
number of deaths resulting from adverse events	0	0	1
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pericarditis			

subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Presyncope			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Oesophagitis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Gallbladder polyp			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	3 / 72 (4.17%)	4 / 75 (5.33%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status asthmaticus			
subjects affected / exposed	0 / 72 (0.00%)	3 / 75 (4.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			

subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic abscess			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 72 (0.00%)	2 / 75 (2.67%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 72 (0.00%)	3 / 75 (4.00%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	0 / 0	0 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pneumonia staphylococcal			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Benra 30 mg q.4 weeks	Placebo	Benra 30 mg q.8 weeks
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 72 (47.22%)	49 / 75 (65.33%)	34 / 73 (46.58%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 72 (2.78%)	2 / 75 (2.67%)	3 / 73 (4.11%)
occurrences (all)	2	2	3
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 72 (6.94%)	4 / 75 (5.33%)	6 / 73 (8.22%)
occurrences (all)	7	4	10
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 72 (1.39%)	2 / 75 (2.67%)	3 / 73 (4.11%)
occurrences (all)	5	2	3
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 72 (1.39%)	3 / 75 (4.00%)	0 / 73 (0.00%)
occurrences (all)	1	3	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	6 / 72 (8.33%)	14 / 75 (18.67%)	1 / 73 (1.37%)
occurrences (all)	11	17	2
Cough			
subjects affected / exposed	2 / 72 (2.78%)	4 / 75 (5.33%)	1 / 73 (1.37%)
occurrences (all)	2	4	1
Dyspnoea			
subjects affected / exposed	2 / 72 (2.78%)	4 / 75 (5.33%)	1 / 73 (1.37%)
occurrences (all)	2	4	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 72 (2.78%)	4 / 75 (5.33%)	2 / 73 (2.74%)
occurrences (all)	2	5	2
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 72 (6.94%)	12 / 75 (16.00%)	8 / 73 (10.96%)
occurrences (all)	7	13	10

Influenza			
subjects affected / exposed	3 / 72 (4.17%)	5 / 75 (6.67%)	1 / 73 (1.37%)
occurrences (all)	3	5	1
Nasopharyngitis			
subjects affected / exposed	11 / 72 (15.28%)	15 / 75 (20.00%)	12 / 73 (16.44%)
occurrences (all)	13	17	14
Oral candidiasis			
subjects affected / exposed	0 / 72 (0.00%)	4 / 75 (5.33%)	0 / 73 (0.00%)
occurrences (all)	0	4	0
Rhinitis			
subjects affected / exposed	2 / 72 (2.78%)	2 / 75 (2.67%)	6 / 73 (8.22%)
occurrences (all)	2	2	7
Sinusitis			
subjects affected / exposed	5 / 72 (6.94%)	8 / 75 (10.67%)	4 / 73 (5.48%)
occurrences (all)	8	11	5
Upper respiratory tract infection			
subjects affected / exposed	4 / 72 (5.56%)	5 / 75 (6.67%)	5 / 73 (6.85%)
occurrences (all)	7	7	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 April 2015	Pulmonary function objectives and change from baseline in blood eosinophils moved from exploratory to secondary objectives; additional secondary endpoints added; change power calculation method from t-test to Wilcoxon rank-sum test; lower eosinophil cut-point for recruitment; clarification of dose titration.
10 February 2016	The timing of database lock and unblinding of CSR was clarified to occur after the last patient had completed the EOT or IPD visit. If, at this time, there were any patients who did not elect to continue in the separate extension study (BORA), and had yet to complete final study-related assessments at the safety follow-up (Visit 15), these assessments were still to be conducted and the data was to be listed separately in an addendum to the CSR.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported