Clinical trial results:
A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3b Study to Evaluate the Onset of Effect and Time Course of Change in Lung Function with Benralizumab in Severe, Uncontrolled Asthma Patients with Eosinophilic Inflammation

Summary

EudraCT number	2016-002094-36
Trial protocol	HU DE
Global end of trial date	30 August 2018

Results information

Result version number	v1 (current)
This version publication date	26 July 2019
First version publication date	26 July 2019

Trial information

Trial identification

Sponsor protocol code	D3250C00038

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02869438
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Vastra Malarehamnen 9, So dertalje, Sweden, 151 85
Public contact	Ubaldo Martin, Global Clinical Lead Benralizumab, AstraZeneca AB, Ubaldo.Martin@astrazeneca.com
Scientific contact	Clinical Study Information, AstraZeneca AB, 46 855 32600, 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	30 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 August 2018
Global end of trial reached?	Yes
Global end of trial date	30 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study is to determine the effect of Benralizumab on the time course of change (onset and maintenance of effect) on lung function

Protection of trial subjects:

The study is performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological samples. Each PI is responsible for providing the ECs/institutional review boards (IRBs) with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca provides this information to the PI so that he/she can meet these reporting requirements. During the study, AstraZeneca representative have regular contacts with the study site, ie, monitoring the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 November 2017
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	Chile: 38
Country: Number of subjects enrolled	Germany: 36
Country: Number of subjects enrolled	Hungary: 41
Country: Number of subjects enrolled	Philippines: 37
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 40
Country: Number of subjects enrolled	United States: 41
Worldwide total number of subjects	233
EEA total number of subjects	77

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)	195
From 65 to 84 years	38
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

721 patients enrolled into D3250C00038 (Solana). 233 participants were randomized to receive treatment with benralizumab 30 mg or placebo. Of the 233 patients randomised, all (100.0%) received treatment with study drug. 118 (50.6%) patients received benralizumab 30 mg and 115 (49.4%) patients received placebo.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Benra 30 mg

Arm description:

12-week treatment period and receive Benra 30 mg at Day 0, Day 28 (±3 days), and Day 56 (±3 days).

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

Dosage and administration details:

30 mg

Arm title	Placebo

Arm description:

12-week treatment period and receive Placebo at Day 0, Day 28 (±3 days), and Day 56 (±3 days).

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

Dosage and administration details:

30 mg

Number of subjects in period 1	Benra 30 mg	Placebo
Started	118	115
Completed	115	113
Not completed	3	2
Consent withdrawn by subject	1	2
Adverse event, non-fatal	1	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Benra 30 mg
Reporting group description:	
12-week treatment period and receive Benra 30 mg at Day 0, Day 28 (±3 days), and Day 56 (±3 days).	
Reporting group title	Placebo
Reporting group description:	
12-week treatment period and receive Placebo at Day 0, Day 28 (±3 days), and Day 56 (±3 days).	

Reporting group values	Benra 30 mg	Placebo	Total
Number of subjects	118	115	233
Age categorical Units: Subjects			
Adults (18-64 years)	97	98	195
From 65-84 years	21	17	38
Age Continuous Units: years			
arithmetic mean	51.9	50.9	
standard deviation	± 13.62	± 12.34	-
Sex: Female, Male Units: Subjects			
Female	74	83	157
Male	44	32	76
Race/Ethnicity, Customized Units: Subjects			
White|	69	67	136
Black or African American|	3	4	7
Asian|	39	40	79
Other|	7	4	11

End points

End points reporting groups

Reporting group title	Benra 30 mg
Reporting group description:	
12-week treatment period and receive Benra 30 mg at Day 0, Day 28 (±3 days), and Day 56 (±3 days).	
Reporting group title	Placebo
Reporting group description:	
12-week treatment period and receive Placebo at Day 0, Day 28 (±3 days), and Day 56 (±3 days).	

Primary: Change from baseline (visit 4) to Day 28 (Visit 8), Day 56 (Visit 9), and Day 84 (Visit 10) in pre-BD FEV1

End point title	Change from baseline (visit 4) to Day 28 (Visit 8), Day 56 (Visit 9), and Day 84 (Visit 10) in pre-BD FEV1
End point description:	
The average over the mean differences between benralizumab and placebo for change from baseline in pre-BD FEV1 is used to determine if the study is positive and to determine maintenance of effect. The first post baseline time point where the p-value for the mean difference between benralizumab and placebo is less than or equal to 0.05 is used to determine time to onset of effect.	
End point type	Primary
End point timeframe:	
From first IP dose to Day 84	

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	115		
Units: Liter				
arithmetic mean (standard deviation)				
Day 28	0.21 (± 0.335)	0.132 (± 0.316)		
Day 56	0.22 (± 0.367)	0.203 (± 0.349)		
Day 84	0.209 (± 0.344)	0.149 (± 0.366)		

Statistical analyses

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0707
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.077
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.007
upper limit	0.161

Notes:

[1] - For Day 28

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.7747
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.013
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.077
upper limit	0.104

Notes:

[2] - For Day 56

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0969
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.079
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.014
upper limit	0.173

Notes:

[3] - For Day 84

Statistical analysis title	Repeated measurement analyses

Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.1558
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.057
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.022
upper limit	0.135

Notes:

[4] - For average of Day 28, 56, 84

Primary: Change from baseline (Visit 4) to end of treatment Day 84 (Visit 10) in Residual volume (RV)

End point title	Change from baseline (Visit 4) to end of treatment Day 84 (Visit 10) in Residual volume (RV)

End point description:

Body plethysmography was performed for sub-study patients. Lung volume subdivisions measures were performed by the investigator or qualified designee according to ATS/ERS guidelines.

End point type	Primary

End point timeframe:

From first IP dose to Day 84

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	22		
Units: Liter				
arithmetic mean (standard deviation)	-0.415 (± 0.609)	-0.208 (± 0.528)		

Statistical analyses

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.2847
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.176

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.505
upper limit	0.153

Notes:

[5] - For Day 84

Secondary: Percent change from baseline to end of treatment in eosinophils counts

End point title	Percent change from baseline to end of treatment in eosinophils counts

End point description:

Percent change from baseline to Day 84

End point type	Secondary

End point timeframe:

From first IP dose to Day 84

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	115		
Units: cell/uL				
arithmetic mean (full range (min-max))	-88.55 (-100 to -12.5)	11.55 (-91.4 to 833.3)		

Statistical analyses

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-101
Confidence interval	
level	95 %
sides	2-sided
lower limit	-118.9
upper limit	-83.06

Notes:

[6] - For Day 84

Secondary: Change from baseline (Visit 4) to post baseline visits in pre-BD FEV1

End point title	Change from baseline (Visit 4) to post baseline visits in pre-BD FEV1

End point description:

Post baseline visits include Day 3, Day 7, Day 14, Day 28, Day 56, Day 84. [Note: Day 28, 56, 84 are presented in the Primary measure.]

End point type	Secondary

End point timeframe:

From first IP dose to Day 84

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	115		
Units: Liter				
arithmetic mean (standard deviation)				
Day 3	0.104 (± 0.223)	0.081 (± 0.269)		
Day 7	0.125 (± 0.229)	0.081 (± 0.263)		
Day 14	0.126 (± 0.3)	0.1 (± 0.287)		

Statistical analyses

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.6384
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.049
upper limit	0.08

Notes:

[7] - For Day 3

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.148
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.046

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.016
upper limit	0.109

Notes:

[8] - For Day 7

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.4959
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.049
upper limit	0.101

Notes:

[9] - For Day 14

Secondary: Change from baseline to post baseline for pre-BD FVC	
End point title	Change from baseline to post baseline for pre-BD FVC
End point description:	
Post baseline visits include Day 3, Day 7, Day 14, Day 28, Day 56, and Day 84.	
End point type	Secondary
End point timeframe:	
From first IP dose to Day 84	

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	115		
Units: Liter				
arithmetic mean (standard deviation)				
Day 3	0.122 (± 0.247)	0.11 (± 0.267)		
Day 7	0.138 (± 0.277)	0.099 (± 0.292)		
Day 14	0.126 (± 0.331)	0.111 (± 0.312)		
Day 28	0.21 (± 0.347)	0.134 (± 0.34)		
Day 56	0.211 (± 0.404)	0.187 (± 0.369)		
Day 84	0.213 (± 0.376)	0.131 (± 0.359)		

Statistical analyses

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.8667
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.062
upper limit	0.073

Notes:
[10] - For Day 3

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.2734
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.041
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.033
upper limit	0.115

Notes:
[11] - For Day 7

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.7252
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.068
upper limit	0.098

Notes:

[12] - For Day 14

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.0976
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.075
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.014
upper limit	0.164

Notes:

[13] - For Day 28

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.6536
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.023
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.077
upper limit	0.122

Notes:

[14] - For Day 56

Statistical analysis title	Repeated measurement analyses

Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.0595
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.092
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	0.188

Notes:

[15] - For Day 84

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.1377
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.063
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.147

Notes:

[16] - For average of Day 28, 56, 84

Secondary: Percentage of pre-BD FEV1 responder

End point title	Percentage of pre-BD FEV1 responder

End point description:

Pre-BD FEV1 responder is defined as change from baseline in FEV1 >=100 ml

End point type	Secondary

End point timeframe:

From first IP dose to Day 84

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	115		
Units: Percentage				
number (not applicable)				
Day 3	48.2	37.4		

Day 7	48.3	42.0		
Day 14	50.0	38.9		
Day 28	57.6	46.9		
Day 56	62.1	55.8		
Day 84	57.9	51.8		

Statistical analyses

Statistical analysis title	Logistic Regression analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.1604
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	2.58

Notes:

[17] - For Day 3

Statistical analysis title	Logistic Regression analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.34
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	2.19

Notes:

[18] - For Day 7

Statistical analysis title	Logistic Regression analyses
Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.0924
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	2.7

Notes:

[19] - For Day 14

Statistical analysis title	Logistic Regression analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.1052
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	2.71

Notes:

[20] - For Day 28

Statistical analysis title	Logistic Regression analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.3271
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	2.21

Notes:

[21] - For Day 56

Statistical analysis title	Logistic Regression analyses

Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.3017
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	2.29

Notes:

[22] - For Day 84

Secondary: Change from baseline in ACQ-6

End point title	Change from baseline 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 first IP dose to Day 84

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	115		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Day 14	-0.989 (± 0.901)	-0.665 (± 0.837)		
Day 28	-1.126 (± 0.947)	-0.693 (± 0.869)		
Day 56	-1.164 (± 1.132)	-0.827 (± 1.023)		
Day 84	-1.355 (± 1.146)	-0.867 (± 1.114)		

Statistical analyses

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.0024
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.293
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.481
upper limit	-0.105

Notes:

[23] - For Day 14

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.0002
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.402
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.609
upper limit	-0.195

Notes:

[24] - For Day 28

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.0117
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.312
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.554
upper limit	-0.07

Notes:

[25] - For Day 56

Statistical analysis title	Repeated measurement analyses

Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	= 0.0004
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.472
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.731
upper limit	-0.213

Notes:

[26] - For Day 84

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	= 0.0002
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.395
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.603
upper limit	-0.188

Notes:

[27] - For average of Day 28, 56, 84

Secondary: Change from baseline in St. George's Respiratory Questionnaire (SGRQ)

End point title	Change from baseline in St. George's Respiratory Questionnaire (SGRQ)

End point description:

The SGRQ is designed to measure health impairment in patients with asthma and COPD. It contains two parts: Part 1 (Questions 1 to 8) covers the patients' recollection of their symptoms over a preceding 4 weeks; Part 2, 42 items, relates to the daily activity and psychosocial impacts of the individual's respiratory condition. Total score is presented as a percentage of overall impairment, in which 100 represents the worst possible health status, while 0 indicates the best.

End point type	Secondary

End point timeframe:

From first IP dose to Day 84

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	115		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Day 28	-16.956 (± 15.51)	-9.444 (± 14.136)		
Day 56	-19.941 (± 21.528)	-13.802 (± 16.705)		
Day 84	-23.343 (± 20.302)	-14.385 (± 18.836)		

Statistical analyses

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-7.229
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.832
upper limit	-3.626

Notes:

[28] - For Day 28

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.0115
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-5.942
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.538
upper limit	-1.346

Notes:

[29] - For Day 56

Statistical analysis title	Repeated measurement analyses

Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	= 0.0004
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-8.599
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.3
upper limit	-3.898

Notes:

[30] - For Day 84

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.0003
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-7.257
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.133
upper limit	-3.38

Notes:

[31] - For average of Day 28, 56, 84

Secondary: Change from baseline to end of treatment in FeNO

End point title	Change from baseline to end of treatment in FeNO

End point description:

Airway inflammation was evaluated via fractional exhaled nitric oxide (FeNO) measurement.

End point type	Secondary

End point timeframe:

From first IP dose to Day 84

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	115		
Units: ppb				
arithmetic mean (standard deviation)	5.92 (± 45.295)	0.05 (± 27.634)		

Statistical analyses

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[32]
P-value	= 0.2825
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	5.414
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.492
upper limit	15.321

Notes:

[32] - For Day 84

Secondary: Change from baseline to end of treatment in total lung capacity (TLC) for sub-study patients

End point title	Change from baseline to end of treatment in total lung capacity (TLC) for sub-study patients

End point description:

Lung volume subdivisions include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC), as well as airway resistance (Raw and SGaw) measurements.

End point type	Secondary

End point timeframe:

From first IP dose to Day 84

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	22		
Units: Liter				
arithmetic mean (standard deviation)	-0.276 (± 0.677)	-0.175 (± 0.418)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to end of treatment in ratio of residual volume (RV) and total lung capacity (TLC) for sub-study patients

End point title	Change from baseline to end of treatment in ratio of residual volume (RV) and total lung capacity (TLC) for sub-study patients

End point description:

Lung volume subdivisions include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC), as well as airway resistance (Raw and SGaw) measurements.

End point type	Secondary

End point timeframe:

From first IP dose to Day 84

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	22		
Units: ratio				
arithmetic mean (standard deviation)	-0.05 (± 0.056)	-0.026 (± 0.087)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to end of treatment in inspiratory capacity (IC) for sub-study patients

End point title	Change from baseline to end of treatment in inspiratory capacity (IC) for sub-study patients

End point description:

Lung volume subdivisions include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC), as well as airway resistance (Raw and SGaw) measurements.

End point type	Secondary

End point timeframe:

From first IP dose to Day 84

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	22		
Units: Liter				
arithmetic mean (standard deviation)	0.119 (± 0.447)	-0.268 (± 0.603)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to end of treatment in functional residual capacity (FRC) for sub-study patients

End point title	Change from baseline to end of treatment in functional residual capacity (FRC) for sub-study patients

End point description:

Lung volume subdivisions include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC), as well as airway resistance (Raw and SGaw) measurements.

End point type	Secondary

End point timeframe:

From first IP dose to Day 84

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	22		
Units: Liter				
arithmetic mean (standard deviation)	-0.394 (± 0.783)	0.093 (± 0.466)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to end of treatment in vital capacity (VC) for sub-study patients

End point title	Change from baseline to end of treatment in vital capacity (VC) for sub-study patients

End point description:

Lung volume subdivisions include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC), as well as airway resistance (Raw and SGaw) measurements.

End point type	Secondary

End point timeframe:

From first IP dose to Day 84

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	22		
Units: Liter				
arithmetic mean (standard deviation)	0.139 (± 0.245)	0.033 (± 0.676)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of IP administration

End point title	Duration of IP administration

End point description:

Duration of IP administration is last IP dose date - first IP dose +1.

End point type	Secondary

End point timeframe:

From first IP to last IP

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	115		
Units: Days				
arithmetic mean (standard deviation)	55.9 (± 7.83)	56.2 (± 7.61)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Serum concentration of Benralizumab

End point title	Serum concentration of Benralizumab[33]

End point description:

PK sample was collected pre-dose at each visit

End point type	Other pre-specified

End point timeframe:

From first IP dose to end of treatment

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is serum concentration with benralizumab, so is only applicable for the active treatment arm

End point values	Benra 30 mg			
Subject group type	Reporting group			
Number of subjects analysed	117			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Baseline|	1.95 (± 0)			
Day 3|	1266.78 (± 199.59)			
Day 7|	1449.47 (± 125.02)			
Day 14|	1317.92 (± 79.53)			
Day 28|	738.47 (± 80.77)			
Day 56|	1015.72 (± 59.74)			
Day 84|	1079.22 (± 73.24)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: PK parameter of Benralizumab (Cmax)

End point title	PK parameter of Benralizumab (Cmax)[34]

End point description:

PK parameters are derived in patients with at least three qualifiable serum PK concentrations post first dose (collected on Day 3, 7, and either 14, or 28)

End point type	Other pre-specified

End point timeframe:

From first IP dose to end of treatment

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is serum concentration with benralizumab, so is only applicable for the active treatment arm

End point values	Benra 30 mg			
Subject group type	Reporting group			
Number of subjects analysed	117			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	1729.6 (± 36.8)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Anti-drug antibody responses

End point title	Anti-drug antibody responses

End point description:

Anti-drug antibody responses at baseline and post baseline, including nAb responses

End point type	Other pre-specified

End point timeframe:

From first IP dose to end of treatment

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	115		
Units: Participants				
ADA prevalence|	7	2		
nAb prevalence|	2	0		
Both baseline and post baseline positive|	1	2		
Only post baseline positive|	5	0		
Only baseline positive|	1	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline to end of treatment in PGI-S

End point title	Change from baseline to end of treatment in PGI-S

End point description:

The patient global impression of severity (PGI-S) is a single item designed to capture the patient's perception of overall symptom severity at the time of the completion using a 6-point categorical response scale (no symptom [0] to very severe symptom [5])

End point type	Other pre-specified

End point timeframe:

From first IP dose to Day 84

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	115		
Units: Score on a scale				
arithmetic mean (standard deviation)	-1.2 (± 1.31)	-0.8 (± 1.21)		

Statistical analyses

Statistical analysis title	Repeated measurement analyses
Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	= 0.012
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.365
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.649
upper limit	-0.081

Notes:

[35] - For Day 84

Other pre-specified: Change from baseline to end of treatment in CGI-C	
End point title	Change from baseline to end of treatment in CGI-C

End point description:

Clinician global impression of change (CGI-C) is used for an overall evaluation of response to treatment. The investigator is asked to rate the degree of change in overall asthma status compare to the start of treatment. A 7-point rating scale is used from 1=very much improved to 7=very much worse.

End point type	Other pre-specified

End point timeframe:

From first IP dose to Day 84

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	115		
Units: Participants				
Very much improved	18	10		
Much improved	39	36		
Minimally improved	39	28		
No change	17	28		
Minimally worse	0	7		
Much worse	0	1		
Very much worse	0	0		
Missing	5	5		

Statistical analyses

Statistical analysis title	Logistic regression analyses

Statistical analysis description:

Responder analysis: responder is defined as Very much improved, improved, and minimally improved.

Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	= 0.0018
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.5
upper limit	5.88

Notes:

[36] - For Day 84

Other pre-specified: Change from baseline to end of treatment in PGI-C

End point title	Change from baseline to end of treatment in PGI-C

End point description:

Patient global impression of change (PGI-C) is used for an overall evaluation of response to treatment. The patient is asked to rate the degree of change in overall asthma status compare to the start of treatment. A 7-point rating scale is used from 1=very much improved to 7=very much worse.

End point type	Other pre-specified

End point timeframe:

From first IP dose to Day 84

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	115		
Units: Participants				
Very much improved	32	17		
Much improved	42	35		
Minimally improved	23	29		
No change	14	27		
Minimally worse	1	4		
Much worse	1	1		
Very much worse	1	0		
Missing	4	2		

Statistical analyses

Statistical analysis title	Logistic regression analyses

Statistical analysis description:

Responder analysis: responder is defined as Very much improved, improved, and minimally improved.

Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	= 0.0107
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.24
upper limit	5.09

Notes:

[37] - For Day 84

Other pre-specified: Change from baseline to end of treatment in specific airway resistance (SGaw) for sub-study patients

End point title	Change from baseline to end of treatment in specific airway resistance (SGaw) for sub-study patients

End point description:

Lung volume subdivisions include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC), as well as airway resistance (Raw and SGaw) measurements.

End point type	Other pre-specified

End point timeframe:

From first IP dose to Day 84

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	22		
Units: 1/(kPa*sec)				
arithmetic mean (standard deviation)	-0.05 (± 0.146)	0.052 (± 0.224)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline to end of treatment in airway resistance (Raw) for sub-study patients

End point title	Change from baseline to end of treatment in airway resistance (Raw) for sub-study patients

End point description:

Lung volume subdivisions include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC), as well as airway resistance (Raw and SGaw) measurements.

End point type	Other pre-specified

End point timeframe:
From first IP dose to Day 84

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	22		
Units: kPa/L/sec				
arithmetic mean (standard deviation)	-0.233 (± 1.509)	-0.2 (± 0.532)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From informed consent form was signed to end of study.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
12-week treatment period and receive Placebo at Day 0, Day 28 (±3 days), and Day 56 (±3 days).	
Reporting group title	Benra 30 mg
Reporting group description:	
12-week treatment period and receive Benra 30 mg at Day 0, Day 28 (±3 days), and Day 56 (±3 days).	

Serious adverse events	Placebo	Benra 30 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 115 (6.09%)	1 / 118 (0.85%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	1 / 115 (0.87%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 115 (0.87%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 115 (0.87%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			

subjects affected / exposed	0 / 115 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 115 (1.74%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 115 (0.87%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 115 (1.74%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Benra 30 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 115 (26.09%)	28 / 118 (23.73%)	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	18 / 115 (15.65%)	11 / 118 (9.32%)	
occurrences (all)	22	11	
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 115 (2.61%)	6 / 118 (5.08%)	
occurrences (all)	3	6	
Nasopharyngitis			
subjects affected / exposed	6 / 115 (5.22%)	8 / 118 (6.78%)	
occurrences (all)	7	9	
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	6 / 115 (5.22%) 8	6 / 118 (5.08%) 7	

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