EU Clinical Trials Register

Clinical trial results:
A Multicentre, Randomised, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) Added to Medium to High-dose Inhaled Corticosteroid Plus Long-acting 2 Agonist in Patients with Uncontrolled Asthma

Summary

EudraCT number	2017-000702-38
Trial protocol	Outside EU/EEA
Global end of trial date	30 January 2023

Results information

Result version number	v1 (current)
This version publication date	30 September 2023
First version publication date	30 September 2023

Trial information

Trial identification

Sponsor protocol code	D3250C00036

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03186209
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Vastra Malarehamnen 9, Sodertalje, Sweden, 151 85
Public contact	Global Clinical Lead, AstraZeneca, +1 8772409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 18772409479, 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	01 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 January 2023
Global end of trial reached?	Yes
Global end of trial date	30 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:	
To evaluate the effect of benralizumab on asthma exacerbations in patients on medium- to high-dose ICS-LABA with uncontrolled asthma	
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	07 September 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	China: 522
Country: Number of subjects enrolled	Taiwan: 14
Country: Number of subjects enrolled	Philippines: 49
Country: Number of subjects enrolled	Korea, Republic of: 110
Worldwide total number of subjects	695
EEA total number of subjects	0

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)	1
Adults (18-64 years)	594
From 65 to 84 years	100
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

695 participants were randomized to received treatment in study D3250C00036 (MIRACLE) with Benralizumab or placebo. All the 695 randomized participants received treatment with study drug. Of the 695 dosed, 348 (50.1%) participants received Benralizumab and 347 (49.9%) pariticipants received placebo.

Pre-assignment

Screening details:

At the first visit, the enrollment visit 1, participants were evaluated regarding the protocol mandated inclusion and exclusion criteria. After enrollment, eligible participants were randomized to either placebo or Benralizumab 30 mg at a 1:1 ratio, administered subcutaneously every 4 weeks for the first 3 doses and then every 8 weeks thereafter.

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, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Benralizumab 30 mg

Arm description:

Benralizumab administered subcutaneously

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, administered every 4 weeks for the first 3 doses and then every 8 weeks after.

Arm title	Placebo

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

Dosage and administration details:

30 mg, administered every 4 weeks for the first 3 doses and then every 8 weeks after.

Number of subjects in period 1	Benralizumab 30 mg	Placebo
Started	348	347
Dosed	348	347
Completed	331	321
Not completed	17	26
Consent withdrawn by subject	11	22
V18 SKIPPED DUE TO LOGISTICS REASON	1	-
Adverse event, non-fatal	4	-
PI DECISION DUE TO LACK OF CRC RESOURCES	-	2
Pregnancy	1	-
Lost to follow-up	-	1
Fail to meet randomization criteria	-	1

Baseline characteristics

Reporting groups

Reporting group title	Benralizumab 30 mg
Reporting group description:	
Benralizumab administered subcutaneously	
Reporting group title	Placebo
Reporting group description:	
Placebo administered subcutaneously	

Reporting group values	Benralizumab 30 mg	Placebo	Total
Number of subjects	348	347	695
Age Categorical Units: Participants			
>=12 - <18 years	1	0	1
>=18 - <65 years	299	295	594
>=65 - <=75	48	52	100
Age Continuous Units: years			
arithmetic mean	51.1	51.0	
standard deviation	± 11.56	± 12.56	-
Sex: Female, Male Units: Participants			
Female	221	207	428
Male	127	140	267
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Non-Hispanic or Latino	348	347	695
Race Units: Subjects			
Asian	348	347	695

End points

End points reporting groups

Reporting group title	Benralizumab 30 mg
Reporting group description:	
Benralizumab administered subcutaneously	
Reporting group title	Placebo
Reporting group description:	
Placebo administered subcutaneously	

Primary: Annual asthma exacerbation rate in patients on medium to high-dose ICS-LABA with uncontrolled asthma for baseline eosinophils >=300/uL

End point title	Annual asthma exacerbation rate in patients on medium to high-dose ICS-LABA with uncontrolled asthma for baseline eosinophils >=300/uL
End point description:	
Annual asthma exacerbation rate over the 48-week treatment period among benralizumab and placebo groups	
End point type	Primary
End point timeframe:	
From randomization through Study Week 48	

End point values	Benralizumab 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	237		
Units: events/patient-year				
least squares mean (confidence interval 95%)	0.49 (0.33 to 0.72)	1.88 (1.35 to 2.61)		

Statistical analyses

Statistical analysis title	Negative Binomial Model
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Negative binomial
Parameter estimate	Rate Ratio
Point estimate	0.26

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	0.36

Notes:

[1] - Multiplicity protected by hierarchy testing procedure. First in line hypothesis testing, requiring p-value <0.05.

Secondary: Change From Baseline at Week 48 in Pre-bronchodilator FEV1 (L) Value for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point title	Change From Baseline at Week 48 in Pre-bronchodilator FEV1 (L) Value for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point description:

Change from baseline at Week 48 in Pre-bronchodilator FEV1 (L)

End point type	Secondary

End point timeframe:

From randomization through Study Week 48

End point values	Benralizumab 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	215	204		
Units: Liter				
arithmetic mean (standard deviation)	0.333 (± 0.4499)	0.103 (± 0.4841)		

Statistical analyses

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.34

Notes:

[2] - Test after significant primary endpoint. Two secondary endpoints (change in FEV1 and total asthma symptom score) using Holm's procedure; smaller p-value to be <0.025, and larger p-value to be <0.05.

Secondary: Change From Baseline at Week 48 in Total Asthma Symptom Score for for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point title	Change From Baseline at Week 48 in Total Asthma Symptom Score for for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point description:

Daytime and nighttime symptoms are reported using a response scale ranging from 0 to 3 where 0 indicates no asthma symptoms. The total asthma symptom score is the sum of the daytime and nighttime scores and ranges from 0 to 6; a decrease in score indicates symptom improvement.

End point type	Secondary

End point timeframe:

From randomization through Study Week 48

End point values	Benralizumab 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	206		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-1.07 (± 1.126)	-0.80 (± 1.129)		

Statistical analyses

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0126 [3]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	-0.05

Notes:

[3] - Test after significant primary endpoint. Two secondary endpoints (change in FEV1 and total asthma symptom score) using Holm's procedure; smaller p-value to be <0.025, and larger p-value to be <0.05.

Secondary: Change from Baseline at Week 48 in Total Asthma Rescue Medication use for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point title	Change from Baseline at Week 48 in Total Asthma Rescue Medication use for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point description:

Change from baseline at week 48 in total rescue medication use (number of puffs/day)

End point type	Secondary

End point timeframe:

From randomization through Study Week 48

End point values	Benralizumab 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	206		
Units: Puffs/day				
arithmetic mean (standard deviation)	-0.85 (± 1.865)	-0.89 (± 2.213)		

Statistical analyses

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1835 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	0.08

Notes:

[4] - Nominal p-value. Not multiplicity protected by testing procedure.

Secondary: Change from Baseline at Week 48 in Morning Peak Expiratory Flow (PEF) for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point title	Change from Baseline at Week 48 in Morning Peak Expiratory Flow (PEF) for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point description:

Change from baseline at week 48 in morning PEF

End point type	Secondary

End point timeframe:

From randomization through Study Week 48

End point values	Benralizumab 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	207		
Units: L/min				
arithmetic mean (standard deviation)	54.194 (± 86.3963)	12.995 (± 68.7947)		

Statistical analyses

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	420
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	38.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	24.24
upper limit	53.07

Notes:

[5] - Nominal p-value. Not multiplicity protected by testing procedure.

Secondary: Change From baseline at Week 48 in the Proportion of Night Awakening Due to Asthma and Requiring rescue medication for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point title	Change From baseline at Week 48 in the Proportion of Night Awakening Due to Asthma and Requiring rescue medication for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point description:

Change from baseline at Week 48 in proportion of night awakening due to asthma and requiring rescue medication

End point type	Secondary

End point timeframe:

From randomization through Study Week 48

End point values	Benralizumab 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	208		
Units: Proportion of nights				
arithmetic mean (standard deviation)	-0.15 (± 0.220)	-0.15 (± 0.260)		

Statistical analyses

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3385 [6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.01

Notes:

[6] - Nominal p-value. Not multiplicity protected by testing procedure.

Secondary: Change from Baseline at Week 48 in Evening Peak Expiratory Flow (PEF) for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point title	Change from Baseline at Week 48 in Evening Peak Expiratory Flow (PEF) for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point description:

Change from baseline at week 48 in evening PEF

End point type	Secondary

End point timeframe:

From randomization through Study Week 48

End point values	Benralizumab 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	209		
Units: L/min				
arithmetic mean (standard deviation)	45.661 (± 85.4642)	7.989 (± 68.0632)		

Statistical analyses

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	426
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	35.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.52
upper limit	50.18

Notes:

[7] - Nominal p-value. Not multiplicity protected by testing procedure.

Secondary: Change From Baseline at Week 48 in Asthma Control Questionnaire 6 (ACQ-6) for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point title	Change From Baseline at Week 48 in Asthma Control Questionnaire 6 (ACQ-6) for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

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.

End point type	Secondary

End point timeframe:

From randomization through Study Week 48

End point values	Benralizumab 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	212		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-1.22 (± 0.901)	-0.79 (± 0.962)		

Statistical analyses

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg v Placebo

Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	-0.28

Notes:

[8] - Nominal p-value. Not multiplicity protected by testing procedure.

Secondary: Time to First Asthma Exacerbation for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point title	Time to First Asthma Exacerbation for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point description:

Time to first asthma exacerbation over 48-week treatment period

End point type	Secondary

End point timeframe:

From randomization through Study Week 48

End point values	Benralizumab 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	237		
Units: Participants	55	125		

Statistical analyses

Statistical analysis title	Cox Regression Model
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.32

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.43

Notes:

[9] - Nominal p-value. Not multiplicity protected by testing procedure.

Secondary: Annual asthma exacerbation rate associated with an emergency room/urgent care visit or a hospitalization for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point title	Annual asthma exacerbation rate associated with an emergency room/urgent care visit or a hospitalization for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point description:

Annual asthma exacerbation rate associated with an emergency room/urgent care visit or a hospitalization over 48-week treatment period

End point type	Secondary

End point timeframe:

From randomization through Study Week 48

End point values	Benralizumab 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	237		
Units: events/patient-year				
least squares mean (confidence interval 95%)	0.06 (0.04 to 0.11)	0.14 (0.09 to 0.20)		

Statistical analyses

Statistical analysis title	Negative Binomial Model
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0222 [10]
Method	Negative binomial
Parameter estimate	Rate ratio
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	0.9

Notes:

[10] - Nominal p-value. Not multiplicity protected by testing procedure.

Secondary: Number and Percentage of Patients With >=1 Asthma Exacerbations among patients who were on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point title	Number and Percentage of Patients With >=1 Asthma Exacerbations among patients who were on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL
End point description:	
Number and percentage of patients with at least one exacerbation over 48-week treatment period	
End point type	Secondary
End point timeframe:	
From randomization through Study Week 48	

End point values	Benralizumab 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	237		
Units: participants				
Number of patients with >=1 asthma exacerbation	55	125		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel Test
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	0.42

Notes:

[11] - Nominal p-value. Not multiplicity protected by testing procedure.

Secondary: Change From Baseline at Week 48 in Total score of St. George's Respiratory Questionnaire (SGRQ) for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point title	Change From Baseline at Week 48 in Total score of St. George's Respiratory Questionnaire (SGRQ) for patients on

high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point description:

The SGRQ is a 50-item PRO instrument developed to measure the HRQoL of patients with airway diseases. The questionnaire is divided into two parts: part 1 consists of 8 items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition. The total score indicates the impact of disease on overall HRQoL. This total score is expressed as a percentage of overall impairment, in which 100 represents the worst possible HRQoL and 0 indicates the best possible HRQoL.

End point type	Secondary

End point timeframe:

From randomization through Study Week 48

End point values	Benralizumab 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	200		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-23.24 (± 20.509)	-14.75 (± 21.838)		

Statistical analyses

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-9.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.79
upper limit	-5.6

Notes:

[12] - Nominal p-value. Not multiplicity protected by testing procedure.

Secondary: The pharmacokinetics (PK) of benralizumab as assessed by trough concentration

End point title	The pharmacokinetics (PK) of benralizumab as assessed by trough concentration

End point description:

PK trough concentrations at each visit

End point type	Secondary

End point timeframe:

week 0, week 24, week 48

End point values	Benralizumab 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	345	0[13]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Week 0	0 (± 0)	()		
Week 24	137.914 (± 432.419)	()		
Week 48	123.476 (± 395.951)	()		

Notes:

[13] - Placebo treated patients are not having pharmacokinetics Benralizumab concentrations analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number and Percentages of Asthma specific Health Care Resource Utilization for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point title	Number and Percentages of Asthma specific Health Care Resource Utilization for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point description:

Asthma specific health care resource utilization over 48-week treatment period.

End point type	Secondary

End point timeframe:

From randomization through Study Week 48

End point values	Benralizumab 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	237		
Units: participants				
Hospitalisations	6	21		
Emergency Department Visits	11	12		
Unscheduled Outpatient Visits	53	99		
Home Visits	1	2		
Telephone Calls	35	71		
Ambulance Transports	2	2		
Advanced Pulmonary Function Test	4	8		

Statistical analyses

No statistical analyses for this end point

Secondary: The immunogenicity of benralizumab as assessed by the presence of anti-drug antibodies (ADAs)

End point title	The immunogenicity of benralizumab as assessed by the presence of anti-drug antibodies (ADAs)

End point description:

Anti-drug antibodies (ADA) responses at baseline and post baseline.

End point type	Secondary

End point timeframe:

Pre-treatment until end of 48-week end of treatment

End point values	Benralizumab 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	348	347		
Units: participants				
ADA positive at any time (ADA prevalence)	58	6		
Treatment-emergent ADA positive(induced/boosted)	58	2		
Treatment-induced ADA positive	56	2		
Treatment-boosted ADA positive	2	0		
ADA positive at both baseline and ≥1 post-baseline	2	2		
ADA positive at baseline only	0	2		
ADA persistently positive	40	1		
ADA transiently positive	16	1		
ADA positive with max titre > median max titre	25	2		
ADA positive with max titre ≤ median max titres	33	4		
nAb prevalence	55	1		
nAb incidence	55	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline at week 48 in blood eosinophil levels for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point title	Percent change from baseline at week 48 in blood eosinophil levels for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils >=300/uL

End point description:

Percent change from baseline at Week 48 in blood eosinophil levels

End point type	Secondary

End point timeframe:

From randomization through Study Week 48

End point values	Benralizumab 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	199		
Units: Percentage				
arithmetic mean (standard deviation)	-80.6 (± 34.65)	42.3 (± 380.86)		

Statistical analyses

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	412
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-119.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-169.78
upper limit	-68.84

Notes:

[14] - Nominal p-value. Not multiplicity protected by testing procedure.

Other pre-specified: Annual asthma exacerbation rate in patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils <300/uL

End point title	Annual asthma exacerbation rate in patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils <300/uL

End point description:

Annual asthma exacerbation rate over the 48-week treatment period among benralizumab and placebo groups

End point type	Other pre-specified

End point timeframe:

From randomization through Study Week 48.

End point values	Benralizumab 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	110		
Units: events/patient-year				
least squares mean (confidence interval 95%)	0.72 (0.49 to 1.06)	0.87 (0.61 to 1.24)		

Statistical analyses

Statistical analysis title	Negative Binomial Model
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4519 [15]
Method	Negative binomial
Parameter estimate	Rate Ratio
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.35

Notes:

[15] - Nominal p-value. Not multiplicity protected by testing procedure.

Other pre-specified: Change From Baseline at Week 48 in Total Asthma Symptom Score for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils <300/uL

End point title	Change From Baseline at Week 48 in Total Asthma Symptom Score for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils <300/uL

End point description:

Daytime and nighttime symptoms are reported using a response scale ranging from 0 to 3 where 0 indicates no asthma symptoms. The total asthma symptom score is the sum of the daytime and nighttime scores and ranges from 0 to 6; a decrease in score indicates symptom improvement.

End point type	Other pre-specified

End point timeframe:

From randomization through Study Week 48

End point values	Benralizumab 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	94		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-0.97 (± 1.260)	-0.75 (± 1.105)		

Statistical analyses

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1589 [16]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	0.08

Notes:

[16] - Nominal p-value. Not multiplicity protected by testing procedure.

Other pre-specified: Change From Baseline at Week 48 in Pre-bronchodilator FEV1 (L) Value for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils <300/uL

End point title	Change From Baseline at Week 48 in Pre-bronchodilator FEV1 (L) Value for patients on medium to high-dose ICS-LABA with uncontrolled asthma and baseline eosinophils <300/uL

End point description:

Change from baseline at Week 48 in Pre-bronchodilator FEV1 (L)

End point type	Other pre-specified

End point timeframe:

From randomization through Study Week 48

End point values	Benralizumab 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	97		
Units: Liter				
arithmetic mean (standard deviation)	0.178 (± 0.4068)	0.045 (± 0.3626)		

Statistical analyses

Statistical analysis title	Mixed Effect Model Repeated Measurement
Comparison groups	Benralizumab 30 mg v Placebo
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0214 [17]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.22

Notes:

[17] - Nominal p-value. Not multiplicity protected by testing procedure.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until last study visit

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo administered subcutaneously

Reporting group title	Benra 30 mg

Reporting group description:

Benralizumab administered subcutaneously

Serious adverse events	Placebo	Benra 30 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	63 / 347 (18.16%)	44 / 348 (12.64%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenolymphoma			
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal papilloma of breast			
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian adenoma			
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian germ cell teratoma benign			

subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Uterine leiomyoma		
subjects affected / exposed	2 / 347 (0.58%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Vascular disorders		
Neurogenic shock		
subjects affected / exposed	1 / 347 (0.29%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Arteriosclerosis		
subjects affected / exposed	1 / 347 (0.29%)	0 / 348 (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		
Food allergy		
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Reproductive system and breast disorders		
Uterine polyp		
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Uterine prolapse		
subjects affected / exposed	1 / 347 (0.29%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders		
Asthma		

subjects affected / exposed	33 / 347 (9.51%)	12 / 348 (3.45%)		
occurrences causally related to treatment / all	0 / 37	0 / 14		
deaths causally related to treatment / all	0 / 0	0 / 0		
Bronchiectasis				
subjects affected / exposed	1 / 347 (0.29%)	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Lung opacity				
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Nasal polyps				
subjects affected / exposed	1 / 347 (0.29%)	3 / 348 (0.86%)		
occurrences causally related to treatment / all	0 / 1	0 / 3		
deaths causally related to treatment / all	0 / 0	0 / 0		
Sinus polyp				
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Vocal cord polyp				
subjects affected / exposed	1 / 347 (0.29%)	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Injury, poisoning and procedural complications				
Femoral neck fracture				
subjects affected / exposed	1 / 347 (0.29%)	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Ankle fracture				
subjects affected / exposed	1 / 347 (0.29%)	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Ligament sprain				

subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	1 / 347 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 347 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 347 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 347 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 347 (0.29%)	0 / 348 (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			

Cerebral infarction				
subjects affected / exposed	1 / 347 (0.29%)	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cerebral ischaemia				
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Ischaemic stroke				
subjects affected / exposed	1 / 347 (0.29%)	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Syncope				
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Eye disorders				
Cataract				
subjects affected / exposed	3 / 347 (0.86%)	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 3	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastrointestinal disorders				
Reflux gastritis				
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Chronic gastritis				
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Abdominal pain				
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

Duodenitis				
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Irritable bowel syndrome				
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Haemorrhoids				
subjects affected / exposed	1 / 347 (0.29%)	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastritis erosive				
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Enteritis				
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Large intestine polyp				
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Hepatobiliary disorders				
Cholecystitis				
subjects affected / exposed	1 / 347 (0.29%)	0 / 348 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Hepatic mass				

subjects affected / exposed	1 / 347 (0.29%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 347 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal mass			
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibromyalgia			
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	2 / 347 (0.58%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthropathy			
subjects affected / exposed	1 / 347 (0.29%)	0 / 348 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteoporosis		
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Periarthritis		
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Rotator cuff syndrome		
subjects affected / exposed	0 / 347 (0.00%)	2 / 348 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Tendonitis		
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Infections and infestations		
Bronchopulmonary aspergillosis		
subjects affected / exposed	1 / 347 (0.29%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Bronchopulmonary aspergillosis allergic		
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Chronic sinusitis		
subjects affected / exposed	0 / 347 (0.00%)	2 / 348 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Nasopharyngitis		
subjects affected / exposed	1 / 347 (0.29%)	0 / 348 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Otitis media		
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pelvic infection		
subjects affected / exposed	1 / 347 (0.29%)	0 / 348 (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	6 / 347 (1.73%)	3 / 348 (0.86%)
occurrences causally related to treatment / all	0 / 6	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia bacterial		
subjects affected / exposed	3 / 347 (0.86%)	3 / 348 (0.86%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia pneumococcal		
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary tuberculosis		
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Sinusitis		
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Upper respiratory tract infection		
subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Asymptomatic COVID-19		

subjects affected / exposed	0 / 347 (0.00%)	1 / 348 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 347 (0.58%)	0 / 348 (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: 3 %

Non-serious adverse events	Placebo	Benra 30 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	269 / 347 (77.52%)	261 / 348 (75.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 347 (3.75%)	7 / 348 (2.01%)	
occurrences (all)	14	7	
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 347 (2.31%)	11 / 348 (3.16%)	
occurrences (all)	14	11	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 347 (2.59%)	18 / 348 (5.17%)	
occurrences (all)	9	22	
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic			
subjects affected / exposed	15 / 347 (4.32%)	22 / 348 (6.32%)	
occurrences (all)	17	41	
Infections and infestations			
Bronchitis			
subjects affected / exposed	27 / 347 (7.78%)	11 / 348 (3.16%)	
occurrences (all)	40	15	
COVID-19			

subjects affected / exposed	6 / 347 (1.73%)	11 / 348 (3.16%)
occurrences (all)	6	11
Nasopharyngitis		
subjects affected / exposed	33 / 347 (9.51%)	28 / 348 (8.05%)
occurrences (all)	48	36
Otitis media		
subjects affected / exposed	8 / 347 (2.31%)	11 / 348 (3.16%)
occurrences (all)	9	11
Pharyngitis		
subjects affected / exposed	13 / 347 (3.75%)	13 / 348 (3.74%)
occurrences (all)	14	13
Rhinitis		
subjects affected / exposed	6 / 347 (1.73%)	13 / 348 (3.74%)
occurrences (all)	9	14
Upper respiratory tract infection		
subjects affected / exposed	120 / 347 (34.58%)	120 / 348 (34.48%)
occurrences (all)	230	200
Urinary tract infection		
subjects affected / exposed	12 / 347 (3.46%)	9 / 348 (2.59%)
occurrences (all)	14	10
Pneumonia		
subjects affected / exposed	16 / 347 (4.61%)	9 / 348 (2.59%)
occurrences (all)	19	13

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 November 2016	1. The SGRQ replaced the AQLQ(s)+12 2. Amended inclusion criteria #8, #13, and #14 3. Amended exclusion criteria #18, #19, #24, and #30 4. Updated text about visit dates and medication restrictions in Section 4, Table 1 5. In Section 7.6.1.1 (background medication), added "medium to high dose" for ICS, and revised duration for ICS-LABA treatment to at least 6 months prior to Visit 1 and during the study 6. Removed the independent adjudication for asthma-related exacerbation 7. Removed the safety objective "Physical Examination"
25 April 2018	In Section 1.4, replaced "Approximately 834 patients will be randomised, among which at least 666 patients (333 patients/arm) patients will be recruited from China" with "Approximately 666 patients will be randomised, among which approximately 534 patients (267 patients/arm) will be recruited from China." Related changes to stratum language in Sections 3.3, 3.10.2, and 8.2 due to the patient sample size change. The sample size justification was also updated.
17 December 2019	1. Amended inclusion criteria #3, #5, and #7 2. Added inclusion criteria #14 ("Pre-bronchodilator FEV1 of < 80% predicted [<90% predicted for patients aged 12 to 17 year] at Visit 2") and #16 ("ACQ-6 score ≥ 1.5 at Visit 2") 3. In Section 3.8.1 and Section 5.1.2, amended language about background medications and about withholding ICS-LABA therapy on the day of scheduled spirometry visits 4. New Section 3.10.5 ("withdrawal due to repeat exacerbations during screening") was added 5. In Section 4, updated ACQ-6 assessment timing 6. In Section 6.3.3, SAE variables were added 7. In Section 7.6.1.1, adjusted language about changing the ICS-LABA dose and documentation
18 December 2020	1. In Sections 1.4 and 3.3, changed percentage of China patients from approximately 80% to at least 70%, and removed specific regions 2. In Sections 3.9 and 7.4, removed the criteria of 2 consecutive doses IP missed for discontinuation; and added statement of how to deal with the cases of a patient missing more than 2 doses within a calendar year, respectively 3. In Section 4.4, new wording added to give guidance on how the study could continue in the event of a serious disruption with details of mitigation that could be employed to ensure study continuity. Language in Appendix G was updated in a similar way 4. In Section 5.3.8, added language to include the possibility of patient testing performed during public health crisis 5. In Section 8.5, added additional analyses to address possible impact of study disruption 6. In Appendix D for anaphylaxis: definition, signs, symptoms and management introduction: changed the wording of appropriate drugs at study sites and updated monitoring timeframe 7. In Appendix G: Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis: new wording was added which gave guidance on how the study could continue in the event of a serious disruption with details of mitigation that could be employed to ensure study continuity

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported