Clinical trial results:
A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Phase 3 Efficacy and Safety Study Of Benralizumab in Patients with Severe Nasal Polyposis (OSTRO)

Summary

EudraCT number	2017-003675-61
Trial protocol	DK AT BE HU PL DE
Global end of trial date	31 July 2020

Results information

Result version number	v1 (current)
This version publication date	12 August 2021
First version publication date	12 August 2021

Trial information

Trial identification

Sponsor protocol code	D3252C00001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03401229
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Vastra Malarehamnen 9, Sodertalje, Sweden,
Public contact	AstraZeneca Information Center, AstraZeneca, +1 8002369933, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 8772409479, information.center@astrazeneca.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2020
Global end of trial reached?	Yes
Global end of trial date	31 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of benralizumab on nasal polyp burden and patient reported nasal blockage (NB).

Protection of trial subjects:

This study is conducted in accordance with the protocol and with the following: Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines; Applicable International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) Guidelines; Applicable laws and regulations.The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated. Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients. Where applicable as per relevant laws and regulations, amendments will also be submitted to, reviewed and approved by regulatory authorities/national competent authorities.

Background therapy:

If a patient was using an alternative intranasal corticosteroids (INCS) product other than mometasone furoate nasal spray (MFNS) prior to visit 1, the Investigator would switch the INCS to MFNS at visit 1. Mometasone furoate (total daily dose of 400mcg) was required daily throughout the study.

Evidence for comparator:

Placebo

Actual start date of recruitment	15 January 2018
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	Austria: 20
Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	Canada: 70
Country: Number of subjects enrolled	Denmark: 51
Country: Number of subjects enrolled	Germany: 65
Country: Number of subjects enrolled	Hungary: 36
Country: Number of subjects enrolled	Poland: 73
Country: Number of subjects enrolled	United States: 78
Worldwide total number of subjects	410
EEA total number of subjects	262

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)	351
From 65 to 84 years	59
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

413 participants were randomized to receive treatment in study D3250C00001 (OSTRO) with benralizumab 30 mg or placebo. Of the 413 patients randomized, 410 (99.3%) received treatment with study drug. 207 (50.5%) patients received benralizumab 30 mg and 203 (49.5%) patients received placebo

Pre-assignment

Screening details:

In OSTRO, at the first visit, ie, the enrollment visit 1, patients were evaluated regarding the protocol mandated inclusion and exclusion criteria. After enrolment, eligible patients entered a 5-week screening/run in period on a stable dose of study provided Mometasone Furoate Nasal Spray (MFNS).

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:

Benra administered every 4 weeks for the first 3 doses - Weeks 0, 4 and 8 and every 8 weeks thereafter - Weeks 16, 24, 32, 40 and 48.

Arm type	Experimental
Investigational medicinal product name	Benralizumab
Investigational medicinal product code	Benra
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Benra administered every 4 weeks for the first 3 doses - Weeks 0, 4 and 8 and every 8 weeks thereafter - Weeks 16, 24, 32, 40 and 48.

Arm title	Placebo

Arm description:

Placebo administered every 4 weeks for the first 3 doses - Weeks 0, 4 and 8 and every 8 weeks thereafter - Weeks 16, 24, 32, 40 and 48.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo administered every 4 weeks for the first 3 doses - Weeks 0, 4 and 8 and every 8 weeks thereafter - Weeks 16, 24, 32, 40 and 48.

Number of subjects in period 1	Benra 30 mg	Placebo
Started	207	203
Completed	167	166
Not completed	40	37
Consent withdrawn by subject	29	26
Adverse event, non-fatal	8	6
COVID-19	-	1
Other	1	3
Lost to follow-up	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Benra 30 mg
Reporting group description:	
Benra administered every 4 weeks for the first 3 doses - Weeks 0, 4 and 8 and every 8 weeks thereafter - Weeks 16, 24, 32, 40 and 48.	
Reporting group title	Placebo
Reporting group description:	
Placebo administered every 4 weeks for the first 3 doses - Weeks 0, 4 and 8 and every 8 weeks thereafter - Weeks 16, 24, 32, 40 and 48.	

Reporting group values	Benra 30 mg	Placebo	Total
Number of subjects	207	203	410
Age categorical Units: Subjects			
Adults (18-64 years)	181	170	351
From 65-84 years	26	33	59
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	50.1	50.2	
standard deviation	± 12.38	± 13.91	-
Sex: Female, Male Units: Participants			
Female	65	82	147
Male	142	121	263
Race/Ethnicity, Customized Units: Subjects			
White	197	190	387
Black or African American	4	8	12
American Indian or Alaska Native	0	1	1
Native Hawaiian or Other Pacific Islander	1	0	1
Asian	3	1	4
Other	2	3	5

Subject analysis sets	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients randomized and receiving any IP irrespective of their protocol adherence and continued participation in the study. Patients are analyzed according to their randomized treatment.	

Reporting group values	Full analysis set		
Number of subjects	410		
Age categorical Units: Subjects			
Adults (18-64 years)	351		

From 65-84 years	59		
85 years and over	0		

Age Continuous Units: Years			
arithmetic mean	50.2		
standard deviation	± 13.14		
Sex: Female, Male Units: Participants			
Female			
Male			
Race/Ethnicity, Customized Units: Subjects			
White			
Black or African American			
American Indian or Alaska Native			
Native Hawaiian or Other Pacific Islander			
Asian			
Other			

End points

End points reporting groups

Reporting group title	Benra 30 mg
Reporting group description:	
Benra administered every 4 weeks for the first 3 doses - Weeks 0, 4 and 8 and every 8 weeks thereafter - Weeks 16, 24, 32, 40 and 48.	
Reporting group title	Placebo
Reporting group description:	
Placebo administered every 4 weeks for the first 3 doses - Weeks 0, 4 and 8 and every 8 weeks thereafter - Weeks 16, 24, 32, 40 and 48.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients randomized and receiving any IP irrespective of their protocol adherence and continued participation in the study. Patients are analyzed according to their randomized treatment.	

Primary: Change from baseline in total NPS at week 40

End point title	Change from baseline in total NPS at week 40
End point description:	
Change from baseline in total nasal polyps score (NPS) at week 40 was defined as the endpoint value at week 40 minus the baseline value. The total NPS was the sum of the right and left nostril scores and maximum total NPS is 8, as evaluated by nasal endoscopy and the left and right score were based on central read with scale from 0 to 4 where higher score reflects heavier bilateral nasal polyp burden. Baseline was the last valid value on or prior to the date of randomization. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids for NP (SCS_NP) were set to missing. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied. In ANCOVA, a hybrid method of WP after NP surgery, WOCF after SCS_NP and multiple imputation (MI) assuming missing at random were used to build the complete imputation datasets for the analysis.	
End point type	Primary
End point timeframe:	
Baseline to week 40	

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	187		
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.36 (± 1.66)	0.17 (± 1.18)		

Statistical analyses

Statistical analysis title	ANCOVA
Statistical analysis description:	
ANCOVA following hybrid WP/WOCF and MI (assuming MAR), adjusting for treatment, baseline score, region (US/Non-US) and baseline comorbid asthma status.	
Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001 [2]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.852
upper limit	-0.289

Notes:

[1] - The primary analysis compared the changes from baseline of benralizumab with placebo. H0: The change from baseline in total NPS and/or the change from baseline in NBS are similar between benralizumab and placebo. H1: Both of the change from baseline in total NPS and the change from baseline in NBS are different between benralizumab and placebo.

[2] - To account for multiplicity, a pre-specified testing strategy was followed to control the overall type I error rate. Both of the co-primary endpoints were tested at 0.01 (two-sided).

Primary: Change from baseline in NBS at week 40

End point title	Change from baseline in NBS at week 40

End point description:

Change from baseline in nasal blockage score (NBS) at week 40 was defined as the endpoint value at week 40 minus the baseline value. The NBS was captured by an item in NPSD. Patients were asked to rate the severity of their worst nasal blockage over the past 24 hours using the following response options: 0–none; 1–mild; 2–moderate; 3–severe. The NBS and the changes from baseline were summarized every two weeks (bi-weekly). Baseline was the average of daily responses from Day –13 to Day 1. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids for NP (SCS_NP) were set to missing. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied. In ANCOVA, a hybrid method of the WP after NP surgery, WOCF after SCS_NP and multiple imputation (MI) assuming missing at random were used to build the complete imputation datasets for the analysis.

End point type	Primary

End point timeframe:

Baseline to week 40

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	181		
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.68 (± 1.02)	-0.41 (± 0.89)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA following hybrid WP/WOCF and MI (assuming MAR), adjusting for treatment, baseline score, region (US/Non-US) and baseline comorbid asthma status

Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0048 [4]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.458
upper limit	-0.083

Notes:

[3] - The primary analysis compared the changes from baseline of benralizumab with placebo. H0: The change from baseline in total NPS and/or the change from baseline in NBS are similar between benralizumab and placebo. H1: Both of the change from baseline in total NPS and the change from baseline in NBS are different between benralizumab and placebo.
[4] - To account for multiplicity, a pre-specified testing strategy was followed to control the overall type I error rate. Both of the co-primary endpoints were tested at
0.01 (two-sided).

Secondary: Change from baseline in SNOT-22 at week 40

End point title	Change from baseline in SNOT-22 at week 40

End point description:

Change from baseline in SinoNasal outcome test (SNOT-22) at week 40 was defined as the endpoint value at week 40 minus the baseline value. The SNOT-22 is a condition specific health-related quality of life assessment which captures patient-reported physical problems, functional limitations, and emotional consequences of sinonasal conditions. The total score is the sum of item scores and has a range from 0 to 110 (higher scores indicate poorer outcomes). Baseline was the last valid value on or prior to the date of randomization. Data collected after NP surgery and/or SCS_NP were set to missing. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied. In ANCOVA, a hybrid method of WP after NP surgery, WOCF after SCS_NP and multiple imputation (MI) assuming missing at random were used to build the complete imputation datasets for the analysis.

End point type	Secondary

End point timeframe:

Baseline to week 40

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	190		
Units: Score on a scale				
arithmetic mean (standard deviation)	-15.2 (± 30.47)	-10.7 (± 31.64)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA following hybrid WP/WOCF and MI (assuming MAR), adjusting for treatment, baseline score,

region (US/Non-US) and baseline comorbid asthma status.

Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	383
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0821 [6]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-5.212
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.087
upper limit	0.664

Notes:

[5] - This endpoint compared the changes from baseline of benralizumab with placebo. H0: The change from baseline in SNOT-22 total score is similar between benralizumab and placebo. H1: The change from baseline in SNOT-22 total score is different between benralizumab and placebo.

[6] - Since both primary endpoints were significant at significant level of 0.01 level, this endpoint was tested at significant level of 0.05.

Secondary: Time to first NP surgery and/or SCS use for NP up to week 56

End point title	Time to first NP surgery and/or SCS use for NP up to week 56

End point description:

The time to first nasal polyposis (NP) surgery and/or systemic corticosteroids (SCS) use for NP up to week 56 was calculated based on the earliest occurrence of NP surgery and/or SCS use for NP and was calculated as follows: Time to first NP surgery and/or SCS use for NP = Earlier of (Start date of first NP surgery, Start date of first SCS use for NP) – date of randomization + 1. For patients who did not experience any surgery or SCS use for NP, the time to event was censored at earlier of (date of their week 56 visit, date of discontinuation).

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	203		
Units: participants	72	91		

Statistical analyses

Statistical analysis title	Cox regression

Statistical analysis description:

A Cox proportional hazards model including covariates treatment group, region (US/Non-US) and baseline comorbid asthma status.

Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.066 [8]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.02

Notes:

[7] - This endpoint compared the rate of incidence of first NP surgery and/or SCS use for NP of benralizumab with placebo. H0: The rate is similar between benralizumab and placebo. H1: the rate is different between benralizumab and placebo. Hazard ratio is benralizumab vs placebo and HR less than 1 indicates longer time to event

[8] - Based on pre-specified testing strategy, this endpoint was not tested for statistical significance and the p-value is considered nominal because test for change from baseline in SNOT-22 at week 40 was not statistically significant.

Secondary: Time to the first NP surgery up to week 56

End point title	Time to the first NP surgery up to week 56

End point description:

The time to first nasal polyposis (NP) surgery up to week 56 was calculated based on the earliest occurrence of NP surgery and was calculated as follows: Time to first NP surgery=Start date of first NP surgery – date of randomization + 1. For patients who did not experience any surgery, the time to event was censored at earlier of (date of their week 56 visit, date of discontinuation).

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	203		
Units: participants	33	37		

Statistical analyses

Statistical analysis title	Cox regression

Statistical analysis description:

A Cox proportional hazards model including covariates treatment group, region (US/Non-US) and baseline comorbid asthma status.

Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.5008 [10]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.36

Notes:

[9] - The endpoint compared the rate of incidence of first NP surgery of benralizumab with placebo. H0: The rate is similar between benralizumab and placebo. H1: the rate is different between benralizumab and placebo. Hazard ratio (HR) is benralizumab vs placebo and HR less than 1 indicates longer time to event

[10] - Based on pre-specified testing strategy, this endpoint was not tested for statistical significance and the p-value was considered nominal.

Secondary: Change from baseline in DSS at week 40

End point title	Change from baseline in DSS at week 40

End point description:

Change from baseline in difficulty with sense of smell (DSS) at week 40 was defined as the endpoint value at week 40 minus the baseline value. The DSS is captured by an item in the NPSD. Severity of worst difficulty with sense of smell over the past 24 hours was rated with response options: 0–none; 1–mild; 2–moderate; 3–severe. The DSS and the changes from baseline were summarized every two weeks (bi-weekly). Baseline was the average of daily responses from Day –13 to Day 1. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids use for NP (SCS_NP) were set to missing. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied. In ANCOVA, a hybrid method of WP after NP surgery, WOCF after SCS_NP and multiple imputation (MI) assuming missing at random were used to build the complete imputation datasets for the analysis.

End point type	Secondary

End point timeframe:

Baseline to week 40

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	181		
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.34 (± 0.74)	-0.16 (± 0.65)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA following hybrid WP/WOCF and MI (assuming MAR), adjusting for treatment, baseline score, region (US/Non-US) and baseline comorbid asthma status

Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.0029 [12]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.218
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.361
upper limit	-0.074

Notes:

[11] - This endpoint compared the changes from baseline DSS score of benralizumab with placebo. H0: The change from baseline in DSS score is similar between benralizumab and placebo. H1: The change from baseline in DSS score is different between benralizumab and placebo.

[12] - Based on pre-specified testing strategy, this endpoint was not tested for statistical significance and the p-value was considered nominal.

Secondary: Change from baseline in NPS at week 56

End point title	Change from baseline in NPS at week 56

End point description:

Change from baseline in total nasal polyps score (NPS) at week 56 was defined as the endpoint value at week 56 minus the baseline value. The total NPS is the sum of the right and left nostril scores, as evaluated by nasal endoscopy and the left and right score are based on central read with scale from 0 to 4 where higher score reflects heavier bilateral nasal polyp burden. Baseline was the last valid value on or prior to the date of randomization. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids for NP (SCS_NP) were set to missing. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied. In ANCOVA, a hybrid method of WP after NP surgery, WOCF after SCS_NP and multiple imputation (MI) assuming missing at random were used to build the complete imputation datasets for the analysis.

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	171		
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.22 (± 1.76)	0.18 (± 1.44)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA following hybrid WP/WOCF and MI (assuming MAR), adjusting for treatment, baseline score, region (US/Non-US) and baseline comorbid asthma status.

Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	332
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.0054 [14]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.475
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	-0.141

Notes:

[13] - This endpoint compared the changes from baseline of benralizumab with placebo. H0: The change from baseline in NPS is similar between benralizumab and placebo. H1: The change from baseline in NPS is different between benralizumab and placebo.

[14] - Based on pre-specified testing strategy, this endpoint was not tested for statistical significance and the p-value was considered nominal.

Secondary: Change from baseline in NBS at week 56

End point title	Change from baseline in NBS at week 56

End point description:

Change from baseline in nasal blockage score (NBS) at week 56 was defined as the endpoint value at week 56 minus the baseline value. The NBS is captured by an item in the NPSD. Patients were asked to rate the severity of their worst nasal blockage over the past 24 hours using the following response options: 0–none; 1–mild; 2–moderate; 3–severe. The NBS and the changes from baseline were summarized every two weeks (bi-weekly). Baseline was the average of daily responses from Day –13 to Day 1. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids for NP (SCS_NP) were set to missing. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied. In ANCOVA, a hybrid method of WP after NP surgery, WOCF after SCS_NP and multiple imputation (MI) assuming missing at random were used to build the complete imputation datasets for the analysis.

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	175		
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.68 (± 1.03)	-0.38 (± 0.91)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA following hybrid WP/WOCF and MI (assuming MAR), adjusting for treatment, baseline score, region (US/Non-US) and baseline comorbid asthma status

Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	354
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.0032 [16]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.287
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.477
upper limit	-0.096

Notes:

[15] - This endpoint compared the changes from baseline of benralizumab with placebo. H0: The change from baseline in NBS is similar between benralizumab and placebo. H1: The change from baseline in NBS is different between benralizumab and placebo.

[16] - Based on pre-specified testing strategy, this endpoint was not tested for statistical significance and the p-value was considered nominal.

Secondary: Change from baseline in SNOT-22 at week 56

End point title	Change from baseline in SNOT-22 at week 56

End point description:

Change from baseline in SinoNasal outcome test (SNOT-22) at week 56 was defined as the endpoint value at week 56 minus the baseline value. The SNOT-22 is a condition specific health-related quality of life assessment which captures patient-reported physical problems, functional limitations, and emotional consequences of sinonasal conditions. The total score is range from 0 to 110 (higher scores indicate poorer outcomes). Baseline was the last valid value on or prior to the date of randomization. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids for NP (SCS_NP) were set to missing. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied. In ANCOVA, a hybrid method of WP after NP surgery, WOCF after SCS_NP and multiple imputation (MI) assuming missing at random were used to build the complete imputation datasets for the analysis.

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	184		
Units: Score on a scale				
arithmetic mean (standard deviation)	-15.1 (± 33.55)	-7.9 (± 33.22)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA following hybrid WP/WOCF and MI (assuming MAR), adjusting for treatment, baseline score, region (US/Non-US) and baseline comorbid asthma status.

Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.0188 [18]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-7.492
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.741
upper limit	-1.243

Notes:

[17] - This endpoint compared the changes from baseline of benralizumab with placebo. H0: The change from baseline in SNOT-22 total score is similar between benralizumab and placebo. H1: The change from baseline in SNOT-22 total score is different between benralizumab and placebo.

[18] - Based on pre-specified testing strategy, this endpoint was not tested for statistical significance and the p-value was considered nominal.

Secondary: Change from baseline in DSS at week 56

End point title	Change from baseline in DSS at week 56

End point description:

Change from baseline in difficulty with sense of smell (DSS) at week 56 was defined as the endpoint value at week 56 minus the baseline value. The DSS is captured by an item in the NPSD with response options: 0–none; 1–mild; 2–moderate; 3–severe to rate the severity of their worst difficulty with sense of smell over past 24 hours. The DSS and the changes from baseline were summarized every two weeks (bi-weekly). Baseline was the average of daily responses from Day –13 to Day 1. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids for NP (SCS_NP) were set to missing. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied. In ANCOVA, a hybrid method of WP after NP surgery, WOCF after SCS_NP and multiple imputation (MI) assuming missing at random were used to build the complete imputation datasets for the analysis.

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	175		
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.39 (± 0.79)	-0.21 (± 0.65)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA following hybrid WP/WOCF and MI (assuming MAR), adjusting for treatment, baseline score, region (US/Non-US) and baseline comorbid asthma status

Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	354
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.0023 [20]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.237
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.389
upper limit	-0.084

Notes:

[19] - This endpoint compared the changes from baseline DSS score of benralizumab with placebo. H0: The change from baseline in DSS score is similar between benralizumab and placebo. H1: The change from baseline in DSS score is different between benralizumab and placebo.

[20] - Based on pre-specified testing strategy, this endpoint was not tested for statistical significance and the p-value was considered nominal.

Secondary: Change from baseline in LMS at EOT/IPD

End point title	Change from baseline in LMS at EOT/IPD

End point description:

Change from baseline in CT Lund Mackay Score (LMS) at end of treatment (EOT)/investigational product discontinuation (IPD) was defined as the endpoint value at EOT/IPD minus the baseline value. The LMS evaluates the patency using a 0-2 scale (0–normal; 1–partial opacification; and 2–total opacification) of each sinus (maxillary, anterior ethmoid, posterior ethmoid, sphenoid, frontal sinus on each side). The osteomeatal complex is graded as 0- not occluded or 2–occluded. The total CT score is the sum of the scores from all the sinus and ranges from 0 to 24. The analysis used the data collected after systemic corticosteroids for nasal polyposis (SCS_NP). A composite strategy was used for NP surgery. If a patient had NP surgery before EOT/IPD CT scan, the data was censored after the time of the first NP surgery and the worst possible value (WP) was imputed in its place.

End point type	Secondary

End point timeframe:

Baseline to EOT/IPD

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81[21]	84[22]		
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.93 (± 5.06)	-0.20 (± 4.20)		

Notes:

[21] - 92 subjects started the arm to the computed tomography (CT) subset.

[22] - 90 subjects started the arm to the computed tomography (CT) subset.

Statistical analyses

Statistical analysis title	Change from baseline in LMS at EOT/IPD, ANCOVA

Statistical analysis description:

ANCOVA following WP (WP for NP surgery), adjusting for treatment, baseline score, region (US/Non-US) and baseline comorbid asthma status.

Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.2375 [24]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.856
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.281
upper limit	0.57

Notes:

[23] - This endpoint compared the changes from baseline LMS score of benralizumab with placebo. H0: The change from baseline in LMS score is similar between benralizumab and placebo. H1: The change from baseline in LMS score is different between benralizumab and placebo.

[24] - Based on pre-specified testing strategy, this endpoint was not tested for statistical significance and the p-value was considered nominal.

Secondary: Proportion of subjects with NP surgery

End point title	Proportion of subjects with NP surgery

End point description:

The proportion of patients who had nasal polyposis (NP) surgery or systemic corticosteroids use for nasal polyposis (SCS_NP) surgery up to week 56 was summarized and analyzed using the Cochran–Mantel–Haenszel test stratified by region (US vs non-US) and baseline comorbid asthma status (yes vs no).

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	203		
Units: participants	33	37		

Statistical analyses

Statistical analysis title	CMH

Statistical analysis description:

The odds ratio estimate was obtained from the Cochran-Mantel-Haenszel test controlling for region (US/non-US) and baseline comorbid asthma status.

Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.5419 [26]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.85

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.43

Notes:

[25] - This endpoint compared the proportion of subjects with NP surgery between benralizumab and placebo. H0: The proportion is similar between benralizumab and placebo. H1: The proportion is different between benralizumab and placebo.

[26] - This endpoint was not a part of the pre-specified testing strategy and was not tested for statistical significance. The p-value was considered nominal.

Secondary: Proportion of subjects with SCS_NP

End point title	Proportion of subjects with SCS_NP

End point description:

The proportion of patients who had systemic corticosteroids (SCS) use for nasal polyposis (NP) surgery up to week 56 was summarized and analyzed using the Cochran–Mantel–Haenszel test stratified by region (US vs non-US) and baseline comorbid asthma status (yes vs no).

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	203		
Units: participants	52	66		

Statistical analyses

Statistical analysis title	CMH

Statistical analysis description:

The odds ratio estimate was obtained from the Cochran-Mantel-Haenszel test controlling for region (US/non-US) and baseline comorbid asthma status.

Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	= 0.0913 [28]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.06

Notes:

[27] - This endpoint compared the proportion of subjects with SCS_NP between benralizumab and placebo. H0: The proportion is similar between benralizumab and placebo. H1: The proportion is different between benralizumab and placebo.

[28] - This endpoint was not a part of the pre-specified testing strategy and was not tested for statistical significance. The p-value was considered nominal.

Secondary: Proportion of subjects with NP surgery or SCS_NP

End point title	Proportion of subjects with NP surgery or SCS_NP

End point description:

The proportion of patients who had nasal polyposis (NP) surgery or systemic corticosteroids use for nasal polyposis (SCS_NP) surgery up to week 56 was summarized and analyzed using the Cochran–Mantel–Haenszel test stratified by region (US vs non-US) and baseline comorbid asthma status (yes vs no).

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	203		
Units: participants	72	91		

Statistical analyses

Statistical analysis title	CMH

Statistical analysis description:

The odds ratio estimate was obtained from the Cochran-Mantel-Haenszel test controlling for region (US/non-US) and baseline comorbid asthma status.

Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.0362 [30]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.97

Notes:

[29] - This endpoint compared the proportion of subjects with NP surgery or SCS_NP between benralizumab and placebo. H0: The proportion is similar between benralizumab and placebo. H1: The proportion is different between benralizumab and placebo.

[30] - This endpoint was not a part of the pre-specified testing strategy and was not tested for statistical significance. The p-value was considered nominal.

Secondary: Time to first SCS_NP up to week 56

End point title	Time to first SCS_NP up to week 56

End point description:

The time to first systemic corticosteroids for use for nasal polyposis (SCS_NP) up to week 56 was calculated based on the earliest occurrence of SCS_ NP and was calculated as follows: Time to first SCS_NP = Earlier of (Start date of first SCS use for NP) – date of randomization + 1. For patients who did not experience any SCS use for NP, the time to event was censored at earlier of (date of their week 56 visit, date of discontinuation). The time to first SCS use for NP surgery was analyzed using a Cox proportional hazard model with treatment arm, region (US vs non-US) and baseline comorbid asthma status (yes vs no) as covariates. A hazard ratio less than 1 indicates a lower rate of incidence for subjects on benra.

End point type	Secondary

End point timeframe:

Baseline week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	203		
Units: participants	52	66		

Statistical analyses

Statistical analysis title	Cox Regression

Statistical analysis description:

A Cox proportional hazards model including covariates treatment group, region (US/Non-US) and baseline comorbid asthma status.

Comparison groups	Benra 30 mg v Placebo
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.1505 [32]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.1

Notes:

[31] - The endpoint compared the rate of incidence of SCS_NP use between benralizumab and placebo. H0: The rate is similar between benralizumab and placebo. H1: the rate is different between benralizumab and placebo. Hazard ratio (HR) is benralizumab vs placebo and HR less than 1 indicates longer time to event

[32] - This endpoint was not a part of the pre-specified testing strategy and was not tested for statistical significance. The p-value was considered nominal.

Secondary: Total number of courses of SCS for NP

End point title	Total number of courses of SCS for NP

End point description:

The total number of courses of systemic corticosteroids (SCS) use for nasal polyposis (NP) was

summarized using descriptive statistics.

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	203		
Units: number of courses				
arithmetic mean (standard deviation)	1.7 (± 0.93)	1.6 (± 0.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total SCS_NP dose (a) used (mg)

End point title	Total SCS_NP dose (a) used (mg)

End point description:

The total systemic corticosteroids (SCS) for nasal polyposis (NP) dose used (mg) was summarized using descriptive statistics.

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207[33]	203		
Units: dose				
arithmetic mean (standard deviation)	1083.2 (± 4044.29)	435.2 (± 441.57)		

Notes:

[33] - Data reported include an outlier with an incorrect dose of betamethasone of 500mg instead of 0.5 mg

Statistical analyses

No statistical analyses for this end point

Secondary: Total duration of SCS_NP (days)

End point title	Total duration of SCS_NP (days)

End point description:

The total duration of systemic corticosteroids (SCS) for nasal polyposis (NP) in days was summarized using descriptive statistics.

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	203		
Units: duration				
arithmetic mean (standard deviation)	17.6 (± 12.45)	20.1 (± 34.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annual SCS_NP use rate comparison by period, negative binomial model

End point title	Annual SCS_NP use rate comparison by period, negative binomial model

End point description:

Annual systemic corticosteroids for nasal polyposis (SCS_NP) use rate =365.25×total number of courses of SCS_NP /total duration of follow-up within the treatment group (days). The estimated annual event rates, absolute differences, rate ratio and the corresponding confidence interval were based on a negative binomial model including covariates treatment group, region (US/non-US) and prior use of SCS_NP with total number of courses of SCS_NP as the outcome and the log of each subject's corresponding follow-up time up to week 56 as an offset variable in the model to adjust for subject's having different exposure times during which the events occur.

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	203		
Units: number of courses for each patient				
arithmetic mean (confidence interval 95%)	0.40 (0.30 to 0.52)	0.50 (0.38 to 0.65)		

Statistical analyses

Statistical analysis title	Negative binomial model

Statistical analysis description:

Model included treatment, US/non-US and prior use of SCS_NP with total number of courses of SCS_NP as outcome and log of follow-up time as an offset

Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	= 0.2189 [35]
Method	Negative Bionomial Model
Parameter estimate	Rate Ratio
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.15

Notes:

[34] - The endpoint compared the rate of SCS_NP use between benralizumab and placebo. H0: The rate is similar between benralizumab and placebo. H1: the rate is different between benralizumab and placebo. Rate ratio is benralizumab vs placebo and Rate ratio less than 1 indicates less likely of SCS_NP use.

[35] - This endpoint was not a part of the pre-specified testing strategy and was not tested for statistical significance. The p-value was considered nominal.

Secondary: Change from baseline in TSS at week 40

End point title	Change from baseline in TSS at week 40

End point description:

Change from baseline in total symptom score (TSS) at week 40 was defined as the endpoint at week 40 minus baseline value. The TSS is defined as sum of first 8 NPSD components. Severity of each nasal symptoms over the past 24 hours is rated using response options: 0–none; 1–mild; 2–moderate; 3–severe. The TSS and the change from baseline were summarized every two weeks (bi-weekly). Baseline was the average of daily TSS responses from Day –13 to Day 1. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids for nasal polyposis (SCS_NP) were set to missing. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied. In ANCOVA, a hybrid method of the WP after NP surgery, WOCF after SCS_NP and multiple imputation (MI) assuming MAR were used to build the complete imputation datasets for the analysis.

End point type	Secondary

End point timeframe:

Baseline to week 40

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	181		
Units: Score on a scale				
arithmetic mean (standard deviation)	-3.20 (± 6.90)	-1.38 (± 6.29)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA following hybrid WP/WOCF and MI (assuming MAR), adjusting for treatment, baseline score, region (US/Non-US) and baseline comorbid asthma status

Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	= 0.0036 [37]
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	-1.854
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.101
upper limit	-0.608

Notes:

[36] - This endpoint compared the changes from baseline score between benralizumab and placebo. H0: The change from baseline score is similar between benralizumab and placebo. H1: The change from baseline score is different between benralizumab and placebo.

[37] - This endpoint was not a part of the pre-specified testing strategy and was not tested for statistical significance. The p-value was considered nominal.

Secondary: Change from baseline in difficulty with sleeping due to nasal symptoms at week 40

End point title	Change from baseline in difficulty with sleeping due to nasal symptoms at week 40

End point description:

Change from baseline in difficulty with sleeping due to nasal symptoms score at week 40 was defined as the endpoint at week 40 minus baseline value. The score was captured by an item in NPSD. The severity of difficulty with sleeping due to nasal symptoms over past 24 hours was rated using options: 0–none; 1–mild; 2–moderate; 3–severe. The score and change from baseline were summarized every two weeks (bi-weekly). Baseline was the average of daily responses from Day –13 to Day 1. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids for nasal polyposis (SCS_NP) were set to missing. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied. In ANCOVA, a hybrid method of the WP after NP surgery, WOCF after SCS_NP and multiple imputation (MI) assuming missing at random were used to build the complete imputation datasets for the analysis

End point type	Secondary

End point timeframe:

Baseline to week 40

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	181		
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.39 (± 1.06)	-0.19 (± 1.03)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA following hybrid WP/WOCF and MI (assuming MAR), adjusting for treatment, baseline score, region (US/Non-US) and baseline comorbid asthma status

Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	= 0.0941 [39]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.166
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.028

Notes:

[38] - This endpoint compared the changes from baseline score between benralizumab and placebo. H0: The change from baseline score is similar between benralizumab and placebo. H1: The change from baseline score is different between benralizumab and placebo.

[39] - This endpoint was not a part of the pre-specified testing strategy and was not tested for statistical significance. The p-value was considered nominal.

Secondary: Change from baseline in difficulty with daily activities due to nasal symptoms at week 40

End point title	Change from baseline in difficulty with daily activities due to nasal symptoms at week 40

End point description:

Change from baseline in difficulty with daily activities due to nasal symptoms score at week 40 was defined as the endpoint at week 40 minus baseline value. The score was captured by an item in NPSD. The severity of difficulty with daily activities due to nasal symptoms over the past 24 hours was rated using options: 0–none; 1–mild; 2–moderate; 3–severe. The score and change from baseline were summarized every two weeks (bi-weekly). Baseline was average of daily responses from Day –13 to Day 1. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids for nasal polyposis (SCS_NP) were set to missing. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied. In ANCOVA, a hybrid method of the WP after NP surgery, WOCF after SCS_NP and multiple imputation (MI) assuming MAR were used to build the complete imputation datasets for the analysis.

End point type	Secondary

End point timeframe:

Baseline to week 40

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	181		
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.35 (± 1.04)	-0.11 (± 0.99)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA following hybrid WP/WOCF and MI (assuming MAR), adjusting for treatment, baseline score, region (US/Non-US) and baseline comorbid asthma status

Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority[40]
P-value	= 0.0246 [41]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.213
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.399
upper limit	-0.027

Notes:

[40] - This endpoint compared the changes from baseline score between benralizumab and placebo. H0: The change from baseline score is similar between benralizumab and placebo. H1: The change from baseline score is different between benralizumab and placebo.

[41] - This endpoint was not a part of the pre-specified testing strategy and was not tested for statistical significance. The p-value was considered nominal.

Secondary: Change from baseline in UPSIT score in males at week 40

End point title	Change from baseline in UPSIT score in males at week 40

End point description:

Change from baseline in University of Pennsylvania Smell Identification Test (UPSIT) score at week 40 was defined as the endpoint value at week 40 minus the baseline value. The UPSIT is quantitative test of olfactory function. Scores were based on number of correctly identified odors (score range 0 to 40). Baseline was the last valid value on or prior to the date of randomization. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids for nasal polyposis (SCS_NP) were set to missing. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied. In ANCOVA, a hybrid method of the WP after NP surgery, WOCF after SCS_NP and multiple imputation (MI) assuming missing at random were used to build the complete imputation datasets for the analysis.

End point type	Secondary

End point timeframe:

Baseline to week 40

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109[42]	89[43]		
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.20 (± 10.29)	0.09 (± 8.05)		

Notes:

[42] - This analysis only includes Male.

[43] - This analysis only includes Female.

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA following hybrid WP/WOCF and MI (assuming MAR), adjusting for treatment, baseline score, region (US/Non-US) and baseline comorbid asthma status

Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority[44]
P-value	= 0.5833 [45]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.672
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.73
upper limit	3.074

Notes:

[44] - This endpoint compared the changes from baseline score between benralizumab and placebo. H0: The change from baseline score is similar between benralizumab and placebo. H1: The change from baseline score is different between benralizumab and placebo.

[45] - This endpoint was not a part of the pre-specified testing strategy and was not tested for statistical significance. The p-value was considered nominal.

Secondary: Change from baseline in UPSIT score in females at week 40

End point title	Change from baseline in UPSIT score in females at week 40

End point description:

Change from baseline in University of Pennsylvania Smell Identification Test (UPSIT) score at week 40 was defined as the endpoint value at week 40 minus the baseline value. The UPSIT is quantitative test of olfactory function. Scores are based on number of correctly identified odors (score range 0 to 40). Baseline was the last valid value on or prior to the date of randomization. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids for nasal polyposis (SCS_NP) were set to missing. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied. In ANCOVA, a hybrid method of the WP after NP surgery, WOCF after SCS_NP and multiple imputation (MI) assuming missing at random were used to build the complete imputation datasets for the analysis.

End point type	Secondary

End point timeframe:

Baseline to week 40

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[46]	74[47]		
Units: Score on a scale				
arithmetic mean (standard deviation)	1.66 (± 8.86)	-1.32 (± 7.66)		

Notes:

[46] - This analysis only includes females.

[47] - This analysis only includes females.

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA following hybrid WP/WOCF and MI (assuming MAR), adjusting for treatment, baseline score, region (US/Non-US) and baseline comorbid asthma status

Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority[48]
P-value	= 0.0619 [49]
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	2.684
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.134
upper limit	5.502

Notes:

[48] - This endpoint compared the changes from baseline score between benralizumab and placebo. H0: The change from baseline score is similar between benralizumab and placebo. H1: The change from baseline score is different between benralizumab and placebo.

[49] - This endpoint was not a part of the pre-specified testing strategy and was not tested for statistical significance. The p-value was considered nominal.

Secondary: Change from baseline in sinus severity score at EOT/IPD

End point title	Change from baseline in sinus severity score at EOT/IPD

End point description:

Change from baseline in sinus severity score at end of treatment (EOT)/investigational product discontinuation (IPD) was defined as the endpoint value at EOT/IPD minus the baseline value. Quantitative assessment of sinus CT image data was used to derive an objective measure of sinus disease burden called sinus severity score. The sinus severity score is defined as (sinus mucosal volume)/(sinus mucosal volume + sinus air volume)×100. A composite strategy was used for NP surgery. If a patient had NP surgery before EOT/IPD CT scan, the data was censored after the time of the first NP surgery and the worst possible value (WP) was imputed in its place. In calculation of summary statistics (mean and standard deviation), the WP for NP surgery rescued subjects was applied. In ANCOVA, following WP (WP for NP surgery rescued subjects), model included treatment, baseline score, region (US/Non-US) and baseline comorbid asthma status.

End point type	Secondary

End point timeframe:

Baseline to EOT/IPD

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	84		
Units: Score on a scale				
arithmetic mean (standard deviation)	-3.48 (± 24.24)	0.79 (± 17.29)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

Following WP (WP for NP surgery rescued subjects), model included treatment, baseline score, region (US/Non-US) and baseline comorbid asthma status

Comparison groups	Benra 30 mg v Placebo

Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[50]
P-value	= 0.102 [51]
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	-5.057
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.129
upper limit	1.015

Notes:

[50] - This endpoint compared the changes from baseline score between benralizumab and placebo. H0: The change from baseline score is similar between benralizumab and placebo. H1: The change from baseline score is different between benralizumab and placebo.

[51] - This endpoint was not a part of the pre-specified testing strategy and was not tested for statistical significance. The p-value was considered nominal.

Secondary: Change from baseline in SF-36v2 physical component summary at week 56

End point title	Change from baseline in SF-36v2 physical component summary at week 56

End point description:

Change from baseline in SF-36v2 physical component summary (PCS) at week 56 was defined as the endpoint value at week 56 minus the baseline value. The Short Form 36-item Health survey (SF-36v2) is a 36-item, self-report survey of functional health and wellbeing, with 4-week recall period. Responses to SF-36v2 were used to compute an 8-domain profile of functional health and well-being scores. PCS score is computed from 8 subscale scores to give a broader metric of physical health-related quality of life. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids for NP (SCS_NP) were set to missing. Non-rescued subjects whose post-baseline observations were all missing were excluded from this analysis. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied.

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	185		
Units: Score on a scale				
arithmetic mean (standard deviation)	-1.557 (± 17.7075)	-3.185 (± 17.4189)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in SF-36v2 mental component summary at week 56

End point title	Change from baseline in SF-36v2 mental component summary at week 56

End point description:

Change from baseline in SF-36v2 mental component summary (MCS) at week 56 was defined as the endpoint value at week 56 minus the baseline value. The Short Form 36-item Health survey (SF-36v2) is a 36-item, self-report survey of functional health and wellbeing, with 4-week recall period. Responses to SF-36v2 were used to compute an 8-domain profile of functional health and well-being scores. MCS score is computed from 8 subscale scores to give a broader metric of mental health-related quality of life. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids for NP (SCS_NP) were set to missing. Non-rescued subjects whose post-baseline observations were all missing were excluded from this analysis. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied.

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	185		
Units: Score on a scale				
arithmetic mean (standard deviation)	-2.263 (± 18.4094)	-4.182 (± 19.3697)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in SF-36v2 physical functioning at week 56

End point title	Change from baseline in SF-36v2 physical functioning at week 56

End point description:

Change from baseline in SF-36v2 physical functioning score at week 56 was defined as the endpoint value at week 56 minus the baseline value. The Short Form 36-item Health survey (SF-36v2) is a 36-item, self-report survey of functional health and wellbeing, with 4-week recall period. Responses to SF-36v2 were used to compute an 8-domain profile of functional health and well-being scores. Physical functioning is one of the 8-domain profile. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids for NP (SCS_NP) were set to missing. Non-rescued subjects whose post-baseline observations were all missing were excluded from this analysis. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied.

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	185		
Units: Score on a scale				
arithmetic mean (standard deviation)	0.080 (± 14.8681)	-0.911 (± 14.6581)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in SF-36v2 role limitations due to physical health at week 56

End point title	Change from baseline in SF-36v2 role limitations due to physical health at week 56

End point description:

Change from baseline in SF-36v2 role limitations due to physical health score at week 56 was defined as the endpoint value at week 56 minus the baseline value. The Short Form 36-item Health survey (SF-36v2) is a 36-item, self-report survey of functional health and wellbeing, with 4-week recall period. Responses to SF-36v2 were used to compute an 8-domain profile of functional health and well-being scores. Role limitations due to physical health is one of the 8-domain profile. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids for NP (SCS_NP) were set to missing. Non-rescued subjects whose post-baseline observations were all missing were excluded from this analysis. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied.

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	185		
Units: Score on a scale				
arithmetic mean (standard deviation)	1.576 (± 13.4610)	0.025 (± 13.3886)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in SF-36v2 bodily pain at week 56

End point title	Change from baseline in SF-36v2 bodily pain at week 56

End point description:

Change from baseline in SF-36v2 bodily pain score at week 56 was defined as the endpoint value at week 56 minus the baseline value. The Short Form 36-item Health survey (SF-36v2) is a 36-item, self-report survey of functional health and wellbeing, with 4-week recall period. Responses to SF-36v2 were used to compute an 8-domain profile of functional health and well-being scores. Bodily pain is one of the 8-domain profile. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids for

NP (SCS_NP) were set to missing. Non-rescued subjects whose post-baseline observations were all missing were excluded from this analysis. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied.

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	185		
Units: Score on a scale				
arithmetic mean (standard deviation)	0.982 (± 15.0935)	-1.066 (± 15.3689)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in SF-36v2 general health perceptions at week 56

End point title	Change from baseline in SF-36v2 general health perceptions at week 56

End point description:

Change from baseline in SF-36v2 general health perceptions score at week 56 was defined as the endpoint value at week 56 minus the baseline value. The Short Form 36-item Health survey (SF-36v2) is a 36-item, self-report survey of functional health and wellbeing, with 4-week recall period. Responses to SF-36v2 were used to compute an 8-domain profile of functional health and well-being scores. General health perceptions is one of the 8-domain profile. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids for NP (SCS_NP) were set to missing. Non-rescued subjects whose post-baseline observations were all missing are excluded from this analysis. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied.

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	185		
Units: Score on a scale				
arithmetic mean (standard deviation)	0.445 (± 14.2295)	-1.064 (± 13.6387)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in SF-36v2 vitality at week 56

End point title	Change from baseline in SF-36v2 vitality at week 56

End point description:

Change from baseline in SF-36v2 vitality score at week 56 was defined as the endpoint value at week 56 minus the baseline value. The Short Form 36-item Health survey (SF-36v2) is a 36-item, self-report survey of functional health and wellbeing, with 4-week recall period. Responses to SF-36v2 were used to compute an 8-domain profile of functional health and well-being scores. Vitality is one of the 8-domain profile. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids for NP (SCS_NP) were set to missing. Non-rescued subjects whose post-baseline observations were all missing were excluded from this analysis. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied.

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	185		
Units: Score on a scale				
arithmetic mean (standard deviation)	1.913 (± 12.9999)	-0.594 (± 13.5861)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in SF-36v2 social functioning at week 56

End point title	Change from baseline in SF-36v2 social functioning at week 56

End point description:

Change from baseline in SF-36v2 social functioning score at week 56 was defined as the endpoint value at week 56 minus the baseline value. The Short Form 36-item Health survey (SF-36v2) is a 36-item, self-report survey of functional health and wellbeing, with 4-week recall period. Responses to SF-36v2 are used to compute an 8-domain profile of functional health and well-being scores. Social functioning is one of the 8-domain profile. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids for NP (SCS_NP) were set to missing. Non-rescued subjects whose post-baseline observations were all missing were excluded from this analysis. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied.

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	185		
Units: Score on a scale				
arithmetic mean (standard deviation)	0.262 (± 15.1786)	-1.247 (± 15.9512)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in SF-36v2 role limitations due to emotional problems at week 56

End point title	Change from baseline in SF-36v2 role limitations due to emotional problems at week 56

End point description:

Change from baseline in SF-36v2 role limitations due to emotional problems score at week 56 was defined as the endpoint value at week 56 minus the baseline value. The Short Form 36-item Health survey (SF-36v2) is a 36-item, self-report survey of functional health and wellbeing, with 4-week recall period. Responses to SF-36v2 were used to compute an 8-domain profile of functional health and well-being scores. Role limitations due to emotional problems is one of the 8-domain profile. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids for NP (SCS_NP) were set to missing. Non-rescued subjects whose post-baseline observations were all missing were excluded from this analysis. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied.

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	185		
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.492 (± 17.1261)	-1.825 (± 16.6618)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in SF-36v2 mental health at week 56

End point title	Change from baseline in SF-36v2 mental health at week 56

End point description:

Change from baseline in SF-36v2 mental health score at week 56 was defined as the endpoint value at week 56 minus the baseline value. The Short Form 36-item Health survey (SF-36v2) is a 36-item, self-report survey of functional health and wellbeing, with 4-week recall period. Responses to SF-36v2 were used to compute an 8-domain profile of functional health and well-being scores. Mental health is one of the 8-domain profile. Data collected after nasal polyposis (NP) surgery and/or systemic corticosteroids

for NP (SCS_NP) were set to missing. Non-rescued subjects whose post-baseline observations were all missing were excluded from this analysis. In calculation of summary statistics (mean and standard deviation), the worst-possible (WP) after NP surgery and worst-observation carried forward (WOCF) after SCS_NP were applied.

End point type	Secondary

End point timeframe:

Baseline to week 56

End point values	Benra 30 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	185		
Units: Score on a scale				
arithmetic mean (standard deviation)	-1.506 (± 16.5930)	-3.308 (± 17.2382)		

Statistical analyses

No statistical analyses for this end point

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	23.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo administered every 4 weeks for the first 3 doses - Weeks 0, 4 and 8 and every 8 weeks thereafter - Weeks 16, 24, 32, 40 and 48.

Reporting group title	Benra 30 mg

Reporting group description:

Benra administered every 4 weeks for the first 3 doses - Weeks 0, 4 and 8 and every 8 weeks thereafter - Weeks 16, 24, 32, 40 and 48.

Serious adverse events	Placebo	Benra 30 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 203 (9.36%)	25 / 207 (12.08%)	
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)			
Adenocarcinoma of appendix			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoma			
subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucoepidermoid carcinoma of salivary gland			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			

subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
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	1 / 203 (0.49%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal leukoplakia			
subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bipolar I disorder			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (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			
Compression fracture			
subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arrhythmia			
subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 203 (0.00%)	2 / 207 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrospinal fistula			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
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	0 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Autoimmune haemolytic anaemia			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic uraemic syndrome			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Rhegmatogenous retinal detachment			
subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coeliac disease			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 203 (0.00%)	2 / 207 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal spasm			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reflux gastritis			

subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
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			
Dermatitis contact			
subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (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			
Hydronephrosis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
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 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis perforated			
subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis bacterial			

subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (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	1 / 203 (0.49%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	0 / 203 (0.00%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 203 (0.49%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Benra 30 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 203 (40.89%)	64 / 207 (30.92%)	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 203 (7.88%)	7 / 207 (3.38%)	
occurrences (all)	18	9	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	30 / 203 (14.78%)	21 / 207 (10.14%)	
occurrences (all)	54	30	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	43 / 203 (21.18%)	37 / 207 (17.87%)	
occurrences (all)	54	57	
Viral upper respiratory tract infection			
subjects affected / exposed	14 / 203 (6.90%)	7 / 207 (3.38%)	
occurrences (all)	15	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 April 2018	Amended inclusion criterion 1 to highlight that nasal polyposis score (NPS) from V2 will be a randomization criterion. Amended to change the requirement for patients being on a stable dose of study provided intranasal corticosteroids (INCS) for 4 weeks prior to randomization to 4 weeks prior to V2. Information about Mometasone Furoate Nasal Spray (MFNS) intolerance was added. Additionally, information about systemic corticosteroids (SCS) intake during screening period and possible extension was added. Amended inclusion criterion 5 to include the requirement of 4 weeks of INCS intake prior V1. Updated Male contraception requirements in inclusion criterion 15. Amended exclusion criterion from 6 months to 3 months. Amended exclusion criterion 5 for asthma exacerbation asthma requiring systemic corticosteroids treatment or hospitalization for treatment asthma from 3 months to 4 weeks prior to V1. Amended exclusion criteria 16 to remove usage of SCS for condition other than short course of NP. Amended exclusion 17 to change the time period for previous use of biologic products from 4 to 6 months and to allow previous use of mepolizumab, reslizumab and dupliumab. Amended exclusion criterion 22 to change the time period for SCS intake from 2 months to 4 weeks prior V1. Note about sustained release steroids or depot injections was added. Amended to allow extension of the screening period and to clarify in which cases re-screening is allowed. Additionally, it was highlighted that patient can be considered for re-screening once under the specific conditions. Amended to remove Information that if patient experienced an asthma exacerbation and/or use of SCS during the screening, he/she should be screen failed.
20 September 2019	Updated of minimum observed mean difference that would be statistically significant at the two-sided alpha 0.05 level from -0.52 to -0.39 in total NPS and from –0.26 to –0.20 in nasal blockage score (NBS). Original critical values for two-sided alpha 0.01 level also included. The statistical methods were amended to add 2 endpoints, change from baseline in University of Pennsylvania smell identification test (UPSIT) score and time to nasal polyposis (NP) surgery and/or SCS use, to the multiplicity testing strategy and to update the power value from 95% to 99% and alpha level from 0.01 to 0.05. Amended to clarify disease under study definition and reporting criteria for adverse events. Amended to specify the estimate of the treatment effect at week 56 for SNOT-22 and UPSIT score for the analyses of key secondary endpoints was based on contrasts from the respective mixed-effects model for repeated measures (MMRM) models.
31 July 2020	Note: The actual protocol amendment date is 05-Aug-2020. The 31-Jul-2020 is the global end of trail date. Multiple changes were made to align the CSP with the amended SAP. These changes include changing the timepoint of primary analysis to week 40, updating the list of key secondary endpoints, updating the primary estimand, reverting power and type I error rate, updating model specification to ANCOVA, and adding a subgroup. Added total symptom score (TSS) as sum of first 8 items of nasal polyposis symptom scores diary (NPSD). Updated language of inclusion in extended follow-up (EFU) period for clarity. Added information about analysis of baseline PK samples and on-treatment PK samples. "A limited number of exploratory biomarkers may be reported in the CSR. Details regarding analyses can be found in the SAP. Any remaining exploratory biomarkers will be reported outside of the CSR." - wording has been added. Additional text regarding Study Conduct Mitigation During evolving SARS-CoV-2 (COVID-19) pandemic or other study disruption has been added to maintain the conduct of study-related activities during crisis, while securing data integrity and patient safety.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

During COVID-19 pandemic, for ongoing patients, patient dosing, scheduled visits, and nasal endoscopies are inevitable impacted. Week 40 was made as the primary timepoint to mitigate the impact of COVID disruptions on the primary endpoint.

Notes: