Clinical trial results:
A multicenter, open-label, safety extension study with Benralizumab for asthmatic adults on inhaled corticosteroid plus long-acting Beta2 agonist

Summary

EudraCT number	2015-005396-25
Trial protocol	GB ES DE CZ PL BG FR
Global end of trial date	18 June 2020

Results information

Result version number	v1 (current)
This version publication date	28 February 2021
First version publication date	28 February 2021

Trial information

Trial identification

Sponsor protocol code	D3250C00037

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02808819
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	23 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 June 2020
Global end of trial reached?	Yes
Global end of trial date	18 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of 2 dosing regimens of benralizumab for adult patients

Protection of trial subjects:

An independent adjudication committee was constituted to provide an independent, external, systematic and unbiased assessment of blinded data to confirm diagnosis of: 1) Investigator-reported non-fatal myocardial infarction, non-fatal stroke (hemorrhagic, ischemic, embolic), as well as cardiovascular deaths and 2) Investigator-reported malignancies during the phase 3 trials. The committee operated in accordance with an Adjudication Committee Charter/Manual of Operations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 11
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Chile: 8
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Turkey: 10
Country: Number of subjects enrolled	Ukraine: 73
Country: Number of subjects enrolled	United States: 86
Country: Number of subjects enrolled	Bulgaria: 11
Country: Number of subjects enrolled	France: 36
Country: Number of subjects enrolled	Germany: 60
Country: Number of subjects enrolled	Poland: 93
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Czechia: 7
Country: Number of subjects enrolled	United Kingdom: 9
Worldwide total number of subjects	446
EEA total number of subjects	216

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)	366
From 65 to 84 years	80
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

447 participants enrolled in MELTEMI, 1 participant from Czech Republic was not treated, thus 446 patients received at least 1 dose of IP. Among these treated participants, 347 were from studies SIROCCO/CALIMA and 99 were from study ZONDA.

Pre-assignment

Screening details:

170 participants from SIROCCO/CALIMA assigned to Benralizumab 30 mg every 4 weeks (q4w) with 1 participant not treated. 178 participants from SIROCCO/CALIMA received Benralizumab every 8 weeks (q8w). 51 participants from ZONDA received Benralizumab q4w. 48 participants from study ZONDA received Benralizumab q8w.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

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

Arm description:

Benralizumab administered subcutaneously every 4 weeks

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

Dosage and administration details:

30 mg

Arm title	Benra 30 mg q.8 weeks

Arm description:

Benralizumab administered subcutaneously every 8 weeks

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

Dosage and administration details:

30 mg

Number of subjects in period 1	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks
Started	220	226
Treated	220	226
Completed	189	195
Not completed	31	31
Adverse event, serious fatal	1	-
Consent withdrawn by subject	10	13
Adverse event, non-fatal	3	4
Pregnancy	1	-
Site terminated by sponsor	2	-
eg. no treatment efficacy on asthma	5	4
Lost to follow-up	1	6
Development of study-specific withdrawal criteria	8	3
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Benra 30 mg q.4 weeks
Reporting group description:	
Benralizumab administered subcutaneously every 4 weeks	
Reporting group title	Benra 30 mg q.8 weeks
Reporting group description:	
Benralizumab administered subcutaneously every 8 weeks	

Reporting group values	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks	Total
Number of subjects	220	226	446
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	177	189	366
From 65-84 years	43	37	80
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	53.5	53.0	
standard deviation	± 12.00	± 11.64	-
Sex: Female, Male Units: Participants			
Female	140	144	284
Male	80	82	162
Race/Ethnicity, Customized Units: Subjects			
White	204	206	410
Black or African	9	13	22
American Asian	5	3	8
Other	2	4	6

End points

End points reporting groups

Reporting group title	Benra 30 mg q.4 weeks
Reporting group description:	
Benralizumab administered subcutaneously every 4 weeks	
Reporting group title	Benra 30 mg q.8 weeks
Reporting group description:	
Benralizumab administered subcutaneously every 8 weeks	

Primary: Change from baseline in Basophils, Full analysis set

End point title	Change from baseline in Basophils, Full analysis set[1]
End point description:	
Change from baseline in hematologic lab parameter of Basophils.	
End point type	Primary
End point timeframe:	
End of Treatment	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: It is a safety long-term extension study. No hypothesis testing planned for the study.

End point values	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	178		
Units: 10^9 cells/L				
arithmetic mean (standard deviation)	0.014 (± 0.0229)	0.012 (± 0.0243)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in Leukocytes, Full analysis set

End point title	Change from baseline in Leukocytes, Full analysis set[2]
End point description:	
Change from baseline in hematologic lab parameter of Leukocytes.	
End point type	Primary
End point timeframe:	
End of Treatment	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: It is a safety long-term extension study. No hypothesis testing planned for the study.

End point values	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	182		
Units: 10^9 cells/L				
arithmetic mean (standard deviation)	-0.254 (± 2.0446)	-0.498 (± 1.7217)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in Lymphocytes, Full analysis set

End point title	Change from baseline in Lymphocytes, Full analysis set[3]

End point description:

Change from baseline in hematologic lab parameter of Lymphocytes.

End point type	Primary

End point timeframe:

End of Treatment

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: It is a safety long-term extension study. No hypothesis testing planned for the study.

End point values	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	178		
Units: 10^9 cells/L				
arithmetic mean (standard deviation)	-0.098 (± 0.5479)	-0.142 (± 0.6544)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in Neutrophils, Full analysis set

End point title	Change from baseline in Neutrophils, Full analysis set[4]

End point description:

Change from baseline in hematologic lab parameter of Neutrophils.

End point type	Primary

End point timeframe:

End of Treatment

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: It is a safety long-term extension study. No hypothesis testing planned for the study.

End point values	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	178		
Units: 10^9 cells/L				
arithmetic mean (standard deviation)	-0.237 (± 1.8765)	-0.392 (± 1.4802)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in Monocytes, Full analysis set

End point title	Change from baseline in Monocytes, Full analysis set[5]

End point description:

Change from baseline in hematologic lab parameter of Monocytes.

End point type	Primary

End point timeframe:

End of Treatment

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: It is a safety long-term extension study. No hypothesis testing planned for the study.

End point values	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	179		
Units: 10^9 cells/L				
arithmetic mean (standard deviation)	0.055 (± 0.1835)	0.056 (± 0.1766)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in Platelets, Full analysis set

End point title	Change from baseline in Platelets, Full analysis set[6]

End point description:

Change from baseline in hematologic lab parameter of Platelets.

End point type	Primary

End point timeframe:

End of Treatment

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: It is a safety long-term extension study. No hypothesis testing planned for the study.

End point values	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	179		
Units: 10^9 cells/L				
arithmetic mean (standard deviation)	9.1 (± 41.72)	11.9 (± 36.13)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in Hematocrit, Full analysis set

End point title	Change from baseline in Hematocrit, Full analysis set[7]

End point description:

Change from baseline in hematologic lab parameter of Hematocrit.

End point type	Primary

End point timeframe:

End of Treatment

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: It is a safety long-term extension study. No hypothesis testing planned for the study.

End point values	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	177		
Units: [ratio]				
arithmetic mean (standard deviation)	-0.002 (± 0.0269)	-0.003 (± 0.0260)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in Erythrocytes, Full analysis set

End point title	Change from baseline in Erythrocytes, Full analysis set[8]

End point description:

Change from baseline in hematologic lab parameter of Erythrocytes.

End point type	Primary

End point timeframe:

End of Treatment

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: It is a safety long-term extension study. No hypothesis testing planned for the study.

End point values	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	183		
Units: 10^12 cells/L				
arithmetic mean (standard deviation)	-0.008 (± 0.2922)	-0.054 (± 0.2614)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in Hemoglobin, Full analysis set

End point title	Change from baseline in Hemoglobin, Full analysis set[9]

End point description:

Change from baseline in hematologic lab parameter of Hemoglobin.

End point type	Primary

End point timeframe:

End of Treatment

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: It is a safety long-term extension study. No hypothesis testing planned for the study.

End point values	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	183		
Units: g/L				
arithmetic mean (standard deviation)	2.6 (± 8.92)	1.2 (± 8.37)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in Alanine Aminotransferase (ALT), Full analysis set

End point title	Change from baseline in Alanine Aminotransferase (ALT), Full analysis set[10]

End point description:

Change from baseline in chemistry test ALT.

End point type	Primary

End point timeframe:

End of Treatment

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: It is a safety long-term extension study. No hypothesis testing planned for the study.

End point values	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	175		
Units: ukat/L				
arithmetic mean (standard deviation)	0.007 (± 0.2060)	0.004 (± 0.2118)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in Aspartate Aminotransferase (AST), Full analysis set

End point title	Change from baseline in Aspartate Aminotransferase (AST), Full analysis set[11]

End point description:

Change from baseline in chemistry test AST.

End point type	Primary

End point timeframe:

End of Treatment

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: It is a safety long-term extension study. No hypothesis testing planned for the study.

End point values	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	175		
Units: ukat/L				
arithmetic mean (standard deviation)	-0.021 (± 0.1258)	-0.018 (± 0.1280)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in Bilirubin, Full analysis set

End point title	Change from baseline in Bilirubin, Full analysis set[12]

End point description:

Change from baseline in chemistry test Bilirubin.

End point type	Primary

End point timeframe:

End of Treatment

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: It is a safety long-term extension study. No hypothesis testing planned for the study.

End point values	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	175		
Units: umol/L				
arithmetic mean (standard deviation)	-0.451 (± 3.0980)	-0.297 (± 3.3972)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with asthma exacerbations during study period

End point title	Number of participants with asthma exacerbations during study period

End point description:

Annual asthma exacerbation rate, where an asthma exacerbation is defined by a worsening of asthma requiring the use of systemic corticosteroids for at least 3 days, and/or an in patient hospitalization, and/or an emergency department or urgent care visit

End point type	Secondary

End point timeframe:

From week 0 to week 184 in study treatment period and through the follow up period (12 weeks from day of last dose)

End point values	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	226		
Units: participants				
Patients with at least one exacerbation	96	97		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who had health care encounter (ie, Hospitalization, Emergency department visits, urgent care visits, and all other outpatient visits due to asthma) during study period

End point title	Number of participants who had health care encounter (ie, Hospitalization, Emergency department visits, urgent care visits, and all other outpatient visits due to asthma) during study period

End point description:

Hospitalizations, Emergency department (ED) visits, urgent care visits and all other outpatient visits due to asthma

End point type	Secondary

End point timeframe:

From week 0 to week 184 in study treatment period and through the follow up period (12 weeks from

day of last dose)

End point values	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	226		
Units: participants				
All healthcare encounters combined	25	28		

Statistical analyses

No statistical analyses for this end point

Secondary: Change of blood eosinophils count

End point title	Change of blood eosinophils count
End point description:	
Change from Baseline to End of Treatment in blood eosinophils count.	
End point type	Secondary
End point timeframe:	
End of Treatment	

End point values	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	178		
Units: cell/uL				
arithmetic mean (standard deviation)	12.3 (± 50.24)	-12.9 (± 212.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Anti-drug antibodies (ADA) responses during the study

End point title	Number of participants with Anti-drug antibodies (ADA) responses during the study
End point description:	
Assessments for the presence of ADA and neutralizing antibody (nAb) throughout study	
End point type	Secondary
End point timeframe:	
From week 0 to week 184 in study treatment period and plus 12 weeks follow up period	

End point values	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	226		
Units: Participants				
Positive at any visit	19	28		
Both baseline and post-baseline positive	11	17		
Only post-baseline positive	7	10		
ADA Persistently Positive	12	21		
ADA Transiently Positive	6	6		
Only baseline positive	1	1		
nAb positive	13	24		
nAb positive in ADA positive participants	13	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of exposure

End point title	Duration of exposure
End point description: Duration of exposure	
End point type	Secondary
End point timeframe: From week 0 to week 184 in study treatment period	

End point values	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	226		
Units: months				
arithmetic mean (standard deviation)	26.35 (± 10.112)	25.36 (± 9.939)		

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	Benra 30 mg q.4 weeks
Reporting group description:	
Benralizumab administered subcutaneously every 4 weeks	
Reporting group title	Benra 30 mg q.8 weeks
Reporting group description:	
Benralizumab administered subcutaneously every 8 weeks	

Serious adverse events	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks	
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 220 (20.00%)	47 / 226 (20.80%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal tract adenoma			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			

subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Silicon granuloma			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	1 / 220 (0.45%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarteritis nodosa			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 220 (0.91%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal complication associated with device			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Non-cardiac chest pain			
subjects affected / exposed	1 / 220 (0.45%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (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			
Uterovaginal prolapse			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (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	9 / 220 (4.09%)	13 / 226 (5.75%)	
occurrences causally related to treatment / all	0 / 15	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			

subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal turbinate hypertrophy			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 220 (0.45%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood lactic acid increased			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (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			
Hip fracture			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Humerus fracture			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 220 (0.00%)	2 / 226 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	2 / 220 (0.91%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural nausea			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (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	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma complication			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Aortic valve stenosis			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (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			
Carotid artery aneurysm			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal fluid leakage			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			

subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient global amnesia			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Hypochromic anaemia			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
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	1 / 220 (0.45%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal tear			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (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	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal stenosis			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral hernia incarcerated			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (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	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			

subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 220 (0.45%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
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			
Angioedema			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
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			
Bone deformity			

subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint range of motion decreased			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament laxity			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 220 (0.45%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
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 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft infection			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	3 / 220 (1.36%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Otitis media			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 220 (0.45%)	2 / 226 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection bacterial			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis bacterial			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 220 (0.45%)	0 / 226 (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			
Gout			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			
subjects affected / exposed	0 / 220 (0.00%)	1 / 226 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	195 / 220 (88.64%)	172 / 226 (76.11%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	14 / 220 (6.36%)	24 / 226 (10.62%)	
occurrences (all)	23	31	
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 220 (3.18%)	2 / 226 (0.88%)	
occurrences (all)	9	2	
Headache			
subjects affected / exposed	32 / 220 (14.55%)	21 / 226 (9.29%)	
occurrences (all)	56	41	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	7 / 220 (3.18%)	8 / 226 (3.54%)	
occurrences (all)	9	10	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 220 (3.64%)	6 / 226 (2.65%)	
occurrences (all)	12	6	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	16 / 220 (7.27%)	20 / 226 (8.85%)	
occurrences (all)	21	40	
Nasal polyps			
subjects affected / exposed	7 / 220 (3.18%)	4 / 226 (1.77%)	
occurrences (all)	10	4	
Rhinitis allergic			
subjects affected / exposed	4 / 220 (1.82%)	8 / 226 (3.54%)	
occurrences (all)	8	12	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	7 / 220 (3.18%)	8 / 226 (3.54%)	
occurrences (all)	7	9	
Back pain			
subjects affected / exposed	11 / 220 (5.00%)	10 / 226 (4.42%)	
occurrences (all)	14	10	
Osteoarthritis			
subjects affected / exposed	10 / 220 (4.55%)	3 / 226 (1.33%)	
occurrences (all)	14	3	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	13 / 220 (5.91%)	8 / 226 (3.54%)	
occurrences (all)	20	10	
Bronchitis			
subjects affected / exposed	23 / 220 (10.45%)	22 / 226 (9.73%)	
occurrences (all)	33	26	
Bronchitis bacterial			
subjects affected / exposed	12 / 220 (5.45%)	9 / 226 (3.98%)	
occurrences (all)	17	13	
Influenza			
subjects affected / exposed	6 / 220 (2.73%)	10 / 226 (4.42%)	
occurrences (all)	6	10	
Nasopharyngitis			
subjects affected / exposed	67 / 220 (30.45%)	64 / 226 (28.32%)	
occurrences (all)	126	112	
Pharyngitis			
subjects affected / exposed	10 / 220 (4.55%)	3 / 226 (1.33%)	
occurrences (all)	19	3	
Rhinitis			
subjects affected / exposed	11 / 220 (5.00%)	3 / 226 (1.33%)	
occurrences (all)	18	3	
Sinusitis			
subjects affected / exposed	17 / 220 (7.73%)	10 / 226 (4.42%)	
occurrences (all)	26	16	
Sinusitis bacterial			

subjects affected / exposed	4 / 220 (1.82%)	7 / 226 (3.10%)	
occurrences (all)	6	10	
Upper respiratory tract infection			
subjects affected / exposed	14 / 220 (6.36%)	8 / 226 (3.54%)	
occurrences (all)	20	12	
Upper respiratory tract infection bacterial			
subjects affected / exposed	10 / 220 (4.55%)	8 / 226 (3.54%)	
occurrences (all)	19	10	
Urinary tract infection			
subjects affected / exposed	7 / 220 (3.18%)	7 / 226 (3.10%)	
occurrences (all)	9	7	
Viral upper respiratory tract infection			
subjects affected / exposed	29 / 220 (13.18%)	19 / 226 (8.41%)	
occurrences (all)	38	21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 July 2017	1. Clarify that for the Q8W regimen, in case one dose was skipped, the next dose must be given within the visit window. If this was not possible, the patient was to be discontinued. 2. Clarify that if a patient chose to discontinue taking investigational product but agreed to return for the IPD and FU visits, then this was not considered a main consent withdrawal and data continued to be collected. If the main informed consent was withdrawn, no further study data and samples were collected. 3. Clarify that withdrawal of informed consent for the use of donated samples by the patient would result in the patient being withdrawn from further study participation. 4. Implement an independent adjudication committee for MACE and malignancies. 5. Multiple revisions were made to the list of restricted and prohibited medications to align with updates made to the BORA protocol.
14 October 2019	Text was updated to reflect that medications would be classified according to the terminology in the latest version of WHODrug Global B3 Format instead of the AstraZeneca Drug Dictionary.

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.

Patients in this study had to complete treatment in predecessor studies. Therefore selection bias may exist. Baseline is defined for this study’s entry value, not the values prior to first Benralizumab dose.

Notes: