Clinical trial results:
PONENTE: A Multicenter, Open-label, Phase 3b Efficacy and Safety Study of Benralizumab 30 mg Administered Subcutaneously to Reduce Oral Corticosteroid Use in Adult Patients with Severe Eosinophilic Asthma on High-Dose Inhaled Corticosteroid plus Long-acting 2 Agonist and Chronic Oral Corticosteroid Therapy

Summary

EudraCT number	2018-000170-30
Trial protocol	DE DK SE ES PL BE GB IT
Global end of trial date	24 March 2022

Results information

Result version number	v1 (current)
This version publication date	31 March 2023
First version publication date	31 March 2023

Trial information

Trial identification

Sponsor protocol code	D3250C00065

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03557307
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	S-151, 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	13 September 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the ability to reduce OCS dose in adult patients with severe eosinophilic asthma treated with benralizumab 30 mg SC

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 oral corticosteroids (OCS) product other than prednisone/prednisolone prior to visit 1, the Investigator would switch to prednisone/prednisolone at visit 1. A stable dose of OCS must have been maintained for ≥4 weeks prior to Visit 1.

Evidence for comparator: -

Actual start date of recruitment	01 August 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 68
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Brazil: 20
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	Colombia: 27
Country: Number of subjects enrolled	Denmark: 21
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 39
Country: Number of subjects enrolled	Italy: 35

Country: Number of subjects enrolled	Mexico: 63
Country: Number of subjects enrolled	Poland: 60
Country: Number of subjects enrolled	Russian Federation: 60
Country: Number of subjects enrolled	Spain: 47
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Taiwan: 22
Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	United States: 62
Worldwide total number of subjects	598
EEA total number of subjects	229

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)	465
From 65 to 84 years	133
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of the 705 patients who provided informed consent and were screened, 598 (84.8%) were eligible to receive Benralizumab 30 mg and entered the study. All 598 (100%) patients received the study drug. 195 of the 538 patients who completed the main study treatment enrolled into PONENTE Long Term Follow Up Substudy.

Pre-assignment

Screening details:

At the first visit, patients were evaluated regarding inclusion and exclusion criteria. Then only those eligible to receive Benra 30 mg were assigned treatment and entered a 4-week induction phase on a stable dose of oral corticosteroids. In Substudy, patients were treated according to healthcare provider discretion with no IP provided by sponsor.

Period 1

Period 1 title	To End of OCS reduction phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Benra 30 mg

Arm description:

Benralizumab 30 mg administered subcutaneously every 4 weeks

Arm type	Experimental
Investigational medicinal product name	Benralizumab
Investigational medicinal product code	
Other name	Fasenra
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Benralizumab 30 mg administered subcutaneously every 4 weeks

Number of subjects in period 1	Benra 30 mg
Started	598
Completed	563
Not completed	35
Adverse event, serious fatal	2
Consent withdrawn by subject	10
Failure to meet inclusion/exclusion criteria	2
Adverse event, non-fatal	7
other	3
Lost to follow-up	5
Protocol deviation	6

Period 2	
Period 2 title	Maintenance phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Benra 30 mg

Arm description:

Benralizumab 30 mg administered subcutaneously every 4 weeks

Arm type	Experimental
Investigational medicinal product name	Benralizumab
Investigational medicinal product code	
Other name	Fasenra
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Benralizumab 30 mg administered subcutaneously every 4 weeks

Number of subjects in period 2	Benra 30 mg
Started	563
Completed	536
Not completed	27
Adverse event, serious fatal	3
Consent withdrawn by subject	2
Adverse event, non-fatal	4
Pregnancy	2
other	3
Lost to follow-up	2
Protocol deviation	11

Period 3	
Period 3 title	Long term follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Asthma treatment as per healthcare provider discretion

Arm description:

Treated as per healthcare provider's discretion. IP or medications were not provided by the sponsor.

Arm type	treated as per healthcare provider's discretion

No investigational medicinal product assigned in this arm

Number of subjects in period 3[1]	Asthma treatment as per healthcare provider discretion
Started	195
Completed	195

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Of the 536 patients who completed main study maintenance phase, only 195 consented and enrolled to the long term follow up substudy.

Baseline characteristics

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

Reporting group values	Benra 30 mg	Total	
Number of subjects	598	598	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	465	465	
From 65-84 years	133	133	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	53.3		
standard deviation	± 13.59	-	
Sex: Female, Male Units: participants			
Female	383	383	
Male	215	215	
Race/Ethnicity, Customized Units: Subjects			
White	475	475	
Black or African American	26	26	
Asian	29	29	
Native Hawaiian or other Pacific Islander	1	1	
American Indian or Alaska Native	46	46	
Other	12	12	
unknown	9	9	

Subject analysis sets	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
All enrolled patients who received at least one dose of benralizumab are included in the FAS, irrespective of their protocol adherence and continued participation in the study.	
Subject analysis set title	Long term follow-up analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who enrolled in Long Term Follow Up substudy

Subject analysis set title	Biologic analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients who have >=50% exposure to any biologic
treatment for asthma from the end of maintenance phase of the main study to the Long Term Follow Up visit

Subject analysis set title	Benra analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients who have >=50% exposure to benralizumab from the end of maintenance phase of the main study to the Long Term follow Up visit, and no previous or concurrent exposure to any other biologic during this period

Reporting group values	Full analysis set	Long term follow-up analysis set	Biologic analysis set
Number of subjects	598	195	78
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	465	166	66
From 65-84 years	133	29	12
85 years and over			
Age Continuous Units: years			
arithmetic mean	53.3	51.9	52.4
standard deviation	± 13.59	± 12.7	± 12.2
Sex: Female, Male Units: participants			
Female	383	115	47
Male	215	80	31
Race/Ethnicity, Customized Units: Subjects			
White	475	151	64
Black or African American	26	8	2
Asian	29	6	3
Native Hawaiian or other Pacific Islander	1	0	0
American Indian or Alaska Native	46	22	5
Other	12	5	1
unknown	9	3	3

Reporting group values	Benra analysis set		
Number of subjects	69		

Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	59		
From 65-84 years	10		
85 years and over			
Age Continuous Units: years			
arithmetic mean	52.5		
standard deviation	± 11.69		
Sex: Female, Male Units: participants			
Female	40		
Male	29		
Race/Ethnicity, Customized Units: Subjects			
White	58		
Black or African American	1		
Asian	2		
Native Hawaiian or other Pacific Islander	0		
American Indian or Alaska Native	5		
Other	1		
unknown	2		

End points

End points reporting groups

Reporting group title	Benra 30 mg
Reporting group description:	
Benralizumab 30 mg administered subcutaneously every 4 weeks	
Reporting group title	Benra 30 mg
Reporting group description:	
Benralizumab 30 mg administered subcutaneously every 4 weeks	
Reporting group title	Asthma treatment as per healthcare provider discretion
Reporting group description:	
Treated as per healthcare provider's discretion. IP or medications were not provided by the sponsor.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
All enrolled patients who received at least one dose of benralizumab are included in the FAS, irrespective of their protocol adherence and continued participation in the study.	
Subject analysis set title	Long term follow-up analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients who enrolled in Long Term Follow Up substudy	
Subject analysis set title	Biologic analysis set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients who have >=50% exposure to any biologic treatment for asthma from the end of maintenance phase of the main study to the Long Term Follow Up visit	
Subject analysis set title	Benra analysis set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients who have >=50% exposure to benralizumab from the end of maintenance phase of the main study to the Long Term follow Up visit, and no previous or concurrent exposure to any other biologic during this period	

Primary: Patients who achieve 100% reduction or a daily OCS dose of <=5mg

End point title	Patients who achieve 100% reduction or a daily OCS dose of <=5mg[1]
End point description:	
Patients who achieve 100% reduction or a daily OCS dose of <=5mg, if reason for no further OCS reduction is Adrenal Insufficiency, that are sustained over at least 4 weeks without worsening of asthma	
End point type	Primary
End point timeframe:	
Baseline to end of OCS reduction phase, an average of approximately 200 days (The duration of the OCS reduction phase may vary based on asthma exacerbations, asthma worsening, HPA integrity , or other safety issues altering the OCS titration schedule.)	

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: This is a single arm study and no comparison between arms is planned.

End point values	Benra 30 mg	Full analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	598	598		
Units: participants	490	490		

Statistical analyses

No statistical analyses for this end point

Primary: Patients who achieve 100% reduction in daily OCS dose

End point title	Patients who achieve 100% reduction in daily OCS dose[2]

End point description:

Patients who achieve 100% reduction in daily OCS dose that are sustained over at least 4 weeks without worsening of asthma

End point type	Primary

End point timeframe:

Baseline to end of OCS reduction phase, an average of approximately 200 days (The duration of the OCS reduction phase may vary based on asthma exacerbations, asthma worsening, HPA integrity , or other safety issues altering the OCS titration schedule.)

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: This is a single arm study and no comparison between arms is planned.

End point values	Benra 30 mg	Full analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	598	598		
Units: participants	376	376		

Statistical analyses

No statistical analyses for this end point

Secondary: Patients who achieve a ≥90%, ≥75%, and ≥50% reduction in daily OCS dose

End point title	Patients who achieve a ≥90%, ≥75%, and ≥50% reduction in daily OCS dose

End point description:

Patients who achieve a ≥90%, ≥75%, and ≥50% reduction in daily OCS dose that are sustained over at least 4 weeks without worsening of asthma

End point type	Secondary

End point timeframe:

Baseline to end of OCS reduction phase, an average of approximately 200 days (The duration of the OCS reduction phase may vary based on asthma exacerbations, asthma worsening, HPA integrity , or other safety issues altering the OCS titration schedule.)

End point values	Benra 30 mg	Full analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	598	598		
Units: participants				
≥90% reduction	383	383		
≥75% reduction	412	412		
≥50% reduction	489	489		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in average daily OCS dose (mg)

End point title	Change from baseline in average daily OCS dose (mg)

End point description:

Change from baseline in average daily OCS dose (mg) from start of OCS reduction to end of the OCS reduction phase

End point type	Secondary

End point timeframe:

Baseline to end of OCS reduction phase, an average of approximately 200 days (The duration of the OCS reduction phase may vary based on asthma exacerbations, asthma worsening, HPA integrity , or other safety issues altering the OCS titration schedule.)

End point values	Benra 30 mg	Full analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	593	593		
Units: mg				
arithmetic mean (confidence interval 95%)	-8.50 (-9.10 to -7.90)	-8.50 (-9.10 to -7.90)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patients who achieve a daily OCS of ≤5mg

End point title	Patients who achieve a daily OCS of ≤5mg

End point description:

Patients who achieve a daily OCS dose of ≤5 mg (regardless of reason for no further OCS reduction), that are sustained over at least 4 weeks without worsening of asthma

End point type	Secondary

End point timeframe:

Baseline to end of OCS reduction phase, an average of approximately 200 days (The duration of the OCS reduction phase may vary based on asthma exacerbations, asthma worsening, HPA integrity , or other safety issues altering the OCS titration schedule.)

End point values	Benra 30 mg	Full analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	598	598		
Units: participants	547	547		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Patients who achieve 100% reduction in daily OCS dose from main study baseline OCS dose to the end of the long term follow up substudy

End point title	Patients who achieve 100% reduction in daily OCS dose from main study baseline OCS dose to the end of the long term follow up substudy

End point description:

Patients who achieve 100% reduction in daily OCS dose that are sustained over at least 4 weeks without worsening of asthma

End point type	Other pre-specified

End point timeframe:

from main study baseline to the end of the long term follow up substudy, an average of approximate 922 days.

End point values	Asthma treatment as per healthcare provider discretion	Long term follow-up analysis set	Biologic analysis set	Benra analysis set
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	195	195	78	69
Units: participants	138	138	60	54

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Patients who achieve a daily OCS dose of ≤5 mg at the end of the long term follow up substudy

End point title	Patients who achieve a daily OCS dose of ≤5 mg at the end of the long term follow up substudy

End point description:

Patients who achieve a daily OCS dose of ≤5 mg (regardless of reason for no further OCS reduction), that are sustained over at least 4 weeks without worsening of asthma

End point type	Other pre-specified

End point timeframe:

from main study baseline to the end of the long term follow up substudy, an average of approximate 922 days.

End point values	Asthma treatment as per healthcare provider discretion	Long term follow-up analysis set	Biologic analysis set	Benra analysis set
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	195	195	78	69
Units: participants	177	177	72	65

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Patients who achieve ≥90%, ≥75%, ≥50% or >0% OCS reduction from main study baseline OCS dose to the end of the long term follow up substudy

End point title	Patients who achieve ≥90%, ≥75%, ≥50% or >0% OCS reduction from main study baseline OCS dose to the end of the long term follow up substudy

End point description:

Patients who achieve a ≥90%, ≥75%, and ≥50% reduction in daily OCS dose that are sustained over at least 4 weeks without worsening of asthma

End point type	Other pre-specified

End point timeframe:

from main study baseline to the end of the long term follow up substudy, an average of approximate 922 days.

End point values	Asthma treatment as per healthcare provider discretion	Long term follow-up analysis set	Biologic analysis set	Benra analysis set
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	195	195	78	69
Units: participants				
>=90% reduction	141	141	61	55
>=75% reduction	151	151	64	58
>=50% reduction	172	172	71	64
>0% reduction	175	175	72	65

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in daily OCS dose (mg) from main study baseline to the end of the long term follow up substudy

End point title	Change in daily OCS dose (mg) from main study baseline to the end of the long term follow up substudy

End point description:

Change in average daily OCS dose (mg) from main study baseline to the end of the long term follow up substudy

End point type	Other pre-specified

End point timeframe:

from main study baseline to the end of the long term follow up substudy, an average of approximate 922 days.

End point values	Asthma treatment as per healthcare provider discretion	Long term follow-up analysis set	Biologic analysis set	Benra analysis set
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	195	195	78	69
Units: mg				
arithmetic mean (confidence interval 95%)	-10.01 (-11.26 to -8.76)	-10.01 (-11.26 to -8.76)	-10.28 (-12.16 to -8.41)	-10.8 (-12.85 to -8.75)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Main study: From first dose of study drug until end of study, with an average of 405 days. Substudy: on-study period, between the date of informed consent for the substudy and the last available visit or contact for a patient, with an average of 18 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Benra 30 mg

Reporting group description:

Benralizumab 30 mg administered subcutaneously every 4 weeks

Reporting group title	Asthma treatment as per healthcare provider discretion

Reporting group description:

Treated as per healthcare provider's discretion. IP or medications were not provided by the sponsor.

Serious adverse events	Benra 30 mg	Asthma treatment as per healthcare provider discretion	
Total subjects affected by serious adverse events			
subjects affected / exposed	89 / 598 (14.88%)	0 / 195 (0.00%)	
number of deaths (all causes)	5	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neurofibroma			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (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 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant glioma			

subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism arterial			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Sudden cardiac death			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Reproductive system and breast disorders			
Breast calcifications			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (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			
Pharyngeal swelling			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			

subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspirin-exacerbated respiratory disease			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	23 / 598 (3.85%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 33	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic rhinosinusitis with nasal polyps			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Oxygen saturation decreased			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (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			
Alcohol poisoning			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (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 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (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	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Multiple fractures			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	2 / 598 (0.33%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	4 / 598 (0.67%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 598 (0.33%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (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			

Apallic syndrome			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery aneurysm			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness postural			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (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	1 / 598 (0.17%)	0 / 195 (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			
Meniere's disease			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Anal fistula			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	2 / 598 (0.33%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (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			
Acute kidney injury			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			

subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (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			
COVID-19			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	2 / 598 (0.33%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	2 / 598 (0.33%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus infection			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected bite			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (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	5 / 598 (0.84%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (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	11 / 598 (1.84%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 11	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	2 / 598 (0.33%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia haemophilus			
subjects affected / exposed	2 / 598 (0.33%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			

subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (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			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (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 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 598 (0.50%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 598 (0.17%)	0 / 195 (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: 3 %

Non-serious adverse events	Benra 30 mg	Asthma treatment as per healthcare provider discretion	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	181 / 598 (30.27%)	0 / 195 (0.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	21 / 598 (3.51%)	0 / 195 (0.00%)	
occurrences (all)	21	0	
Nervous system disorders			
Headache			
subjects affected / exposed	29 / 598 (4.85%)	0 / 195 (0.00%)	
occurrences (all)	38	0	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	33 / 598 (5.52%)	0 / 195 (0.00%)	
occurrences (all)	34	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	64 / 598 (10.70%)	0 / 195 (0.00%)	
occurrences (all)	92	0	
Sinusitis			
subjects affected / exposed	19 / 598 (3.18%)	0 / 195 (0.00%)	
occurrences (all)	22	0	
Viral upper respiratory tract infection			
subjects affected / exposed	28 / 598 (4.68%)	0 / 195 (0.00%)	
occurrences (all)	31	0	
Upper respiratory tract infection			
subjects affected / exposed	25 / 598 (4.18%)	0 / 195 (0.00%)	
occurrences (all)	28	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 January 2019	Clarified study design, objectives, statistical methods, inclusion/exclusion criteria and Study Plan and Timing of procedures.
06 November 2019	The cortisol test pathway has been strengthened. All reference to the sputum substudy has been deleted. The sub-study was terminated due to low enrollment rate. Sputum samples already collected at the time of this amendment will not be analyzed, and will be destroyed.
17 October 2020	This amendment includes the addition of a long-term follow-up visit 12 to 18 months after end of PONENTE treatment period where we will retrospectively collect data to understand changes in OCS dose and other background asthma therapy, and occurrence of asthma exacerbations under real-world conditions. We will also evaluate the recovery from adrenal insufficiency (AI) and the long-term impact of OCS reduction achieved during PONENTE study on the glucocorticoid toxicity.

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, and scheduled visits are inevitably impacted, but the primary endpoint was not impacted.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34619104

http://www.ncbi.nlm.nih.gov/pubmed/31579676

http://www.ncbi.nlm.nih.gov/pubmed/35896216

http://www.ncbi.nlm.nih.gov/pubmed/36769635

http://www.ncbi.nlm.nih.gov/pubmed/35246123