Clinical trial results:
SHAMAL: A Multicentre, Randomised, Open-Label, Parallel-Group, Active-Controlled, Phase IV Study to Assess the Reduction of Daily Maintenance ICS/LABA Treatment Towards Anti-Inflammatory Reliever Treatment in Patients with Severe Eosinophilic Asthma Treated with Benralizumab

Summary

EudraCT number	2019-001924-37
Trial protocol	GB DE FR IT
Global end of trial date	31 January 2023

Results information

Result version number	v1 (current)
This version publication date	14 February 2024
First version publication date	14 February 2024

Trial information

Trial identification

Sponsor protocol code	D3250C00072

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04159519
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca Clinical study Information Center
Sponsor organisation address	Södertälje, Södertälje, Sweden, 151 85
Public contact	AstraZeneca Clinical study Information Center, AstraZeneca Clinical study Information Center, +1 8772409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca Clinical study Information Center, +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	28 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the potential for benralizumab-treated patients to reduce Symbicort maintenance treatment while maintaining asthma symptom control.

Protection of trial subjects:

The clinical study protocol (CSP) and participant informed consent documents were reviewed and approved by the institutional review board/independent ethics committee before the study was initiated. This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics. The Principal Investigator at each study site explained the nature of the study to the patient and answered all questions regarding the study. Patients were informed that their participation was voluntary, and they were free to refuse to participate and withdraw their consent at any time and for any reason during the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 July 2020
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	France: 34
Country: Number of subjects enrolled	Germany: 72
Country: Number of subjects enrolled	Italy: 24
Country: Number of subjects enrolled	United Kingdom: 38
Worldwide total number of subjects	168
EEA total number of subjects	130

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	114
From 65 to 84 years	54
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted between 27 July 2020 and 31 January 2023.

Pre-assignment

Screening details:

The study included a screening period and run-in period of 4-8 weeks . The 208 were enrolled and entered screening and run-in period, during which patients received benralizumab with high-dose Symbicort. At Week 0, patients meeting the randomization criteria were randomized into treatment reduction or reference arms.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment reduction

Arm description:

Patients received benralizumab 30 mg every 8 weeks (Q8W) during the study period, and high-dose Symbicort maintenance 400/12 µg ×2 inhalations BID + Ventolin (salbutamol 100 µg) reliever as needed (PRN), tapering to, medium-dose Symbicort 200/6 µg ×2 inhalations BID maintenance + Symbicort 200/6 µg reliever PRN, low dose Symbicort 200/6 µg x 1 inhalation BID maintenance + Symbicort 200/6 µg reliever PRN; or Symbicort 200/6 µg reliever only, as per tapering scheme and depending on the degree of asthma control). The reduction period in this arm lasted for 32 weeks.

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

Dosage and administration details:

Patients received benralizumab 30 mg/mL, 1 mL fill volume via subcutaneous injection every 8 weeks during the study period.

Investigational medicinal product name	Ventolin®
Investigational medicinal product code	
Other name	Salbutamol
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

Patients received salbutamol sulfate 100 µg per inhalation in the screening/run-in phase as needed.

Investigational medicinal product name	Symbicort®
Investigational medicinal product code	
Other name	Budesonide/formoterol
Pharmaceutical forms	Inhalation solution, Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Patients received budesonide 400 µg/formoterol fumarate 12 µg per inhalation (2 inhalations) BID as maintenance, and reducing to budesonide 200 µg/formoterol fumarate 6 µg per inhalation (1 or 2 inhalations) BID as maintenance and reliever as needed, or as reliever only.

Arm title	Reference

Arm description:

Patients received benralizumab 30 mg Q8W + high-dose Symbicort® 400/12 µg maintenance × 2 inhalations BID + Ventolin® (salbutamol 100 µg) reliever PRN therapy. Eligible patients randomised to the reference arm continued on high-dose Symbicort® maintenance treatment and Ventolin® reliever treatment.

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

Dosage and administration details:

Patients received benralizumab 30 mg/mL, 1 mL fill volume via subcutaneous injection every 8 weeks during the study period.

Investigational medicinal product name	Ventolin®
Investigational medicinal product code	
Other name	Salbutamol
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

Patients received salbutamol sulfate 100 µg per inhalation as needed.

Investigational medicinal product name	Symbicort®
Investigational medicinal product code	
Other name	Budesonide/formoterol
Pharmaceutical forms	Inhalation solution, Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Patients received budesonide 400 µg/formoterol fumarate 12 µg per inhalation (2 inhalations) BID as maintenance.

Number of subjects in period 1	Treatment reduction	Reference
Started	125	43
Completed	117	37
Not completed	8	6
Consent withdrawn by subject	4	4
Adverse event, non-fatal	1	1
Discontinued from study	1	-
Lack of efficacy	1	-
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment reduction
Reporting group description:	
Patients received benralizumab 30 mg every 8 weeks (Q8W) during the study period, and high-dose Symbicort maintenance 400/12 µg ×2 inhalations BID + Ventolin (salbutamol 100 µg) reliever as needed (PRN), tapering to, medium-dose Symbicort 200/6 µg ×2 inhalations BID maintenance + Symbicort 200/6 µg reliever PRN, low dose Symbicort 200/6 µg x 1 inhalation BID maintenance + Symbicort 200/6 µg reliever PRN; or Symbicort 200/6 µg reliever only, as per tapering scheme and depending on the degree of asthma control). The reduction period in this arm lasted for 32 weeks.	
Reporting group title	Reference
Reporting group description:	
Patients received benralizumab 30 mg Q8W + high-dose Symbicort® 400/12 µg maintenance × 2 inhalations BID + Ventolin® (salbutamol 100 µg) reliever PRN therapy. Eligible patients randomised to the reference arm continued on high-dose Symbicort® maintenance treatment and Ventolin® reliever treatment.	

Reporting group values	Treatment reduction	Reference	Total
Number of subjects	125	43	168
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)	82	32	114
From 65-84 years	43	11	54
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	58.1	56.5	
standard deviation	± 12.44	± 11.70	-
Sex: Female, Male Units: Participants			
Female	69	20	89
Male	56	23	79

End points

End points reporting groups

Reporting group title	Treatment reduction

Reporting group description:

Patients received benralizumab 30 mg every 8 weeks (Q8W) during the study period, and high-dose Symbicort maintenance 400/12 µg ×2 inhalations BID + Ventolin (salbutamol 100 µg) reliever as needed (PRN), tapering to, medium-dose Symbicort 200/6 µg ×2 inhalations BID maintenance + Symbicort 200/6 µg reliever PRN, low dose Symbicort 200/6 µg x 1 inhalation BID maintenance + Symbicort 200/6 µg reliever PRN; or Symbicort 200/6 µg reliever only, as per tapering scheme and depending on the degree of asthma control). The reduction period in this arm lasted for 32 weeks.

Reporting group title	Reference

Reporting group description:

Patients received benralizumab 30 mg Q8W + high-dose Symbicort® 400/12 µg maintenance × 2 inhalations BID + Ventolin® (salbutamol 100 µg) reliever PRN therapy. Eligible patients randomised to the reference arm continued on high-dose Symbicort® maintenance treatment and Ventolin® reliever treatment.

Primary: Proportion of patients who reduced their Symbicort® maintenance dose at the end of the reduction period

End point title	Proportion of patients who reduced their Symbicort® maintenance dose at the end of the reduction period[1][2]

End point description:

Proportion of patients with non-missing Week 32 who reduced their Symbicort® maintenance dose at the end of the reduction period (Week 32) to: a) Medium-dose Symbicort® maintenance and reliever therapy (SMART), or b) Low-dose SMART, or c) Symbicort® anti-inflammatory reliever only. The full analysis set (FAS) population included for this endpoint, all randomised patients, irrespective of their protocol adherence and continued participation in the study.

End point type	Primary

End point timeframe:

At Week 32

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: No statistical analysis was performed.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was performed.

End point values	Treatment reduction			
Subject group type	Reporting group			
Number of subjects analysed	119			
Units: Proportion				
number (confidence interval 95%)				
Medium-dose SMART	0.151 (0.0922 to 0.2285)			
Low-dose SMART	0.168 (0.1058 to 0.2476)			
Symbicort® reliever-only dose	0.605 (0.5113 to 0.6934)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Asthma control questionnaire-5 item (ACQ-5) score at the end of the reduction period

End point title	Change from baseline in Asthma control questionnaire-5 item (ACQ-5) score at the end of the reduction period

End point description:

Change from baseline in the ACQ-5 patient reported outcome. This instrument contains 5 asthma symptom questions, rated from 0 (total control) to 6 (severely uncontrolled). The ACQ-5 score is the mean of the responses. Mean scores ≤0.75 indicate well controlled, >0.75 and <1.5 indicate partly controlled and ≥1.5 indicate not well controlled asthma. The FAS population included for this endpoint, all randomised patients, irrespective of their protocol adherence and continued participation in the study.

End point type	Secondary

End point timeframe:

Week 0 (baseline) and at Week 32

End point values	Treatment reduction	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	38		
Units: Change from baseline in score				
least squares mean (standard error)	0.1617 (± 0.0393)	0.0555 (± 0.0677)		

Statistical analyses

Statistical analysis title	Comparison with reference arm
Statistical analysis description: Comparison with reference arm	
Comparison groups	Treatment reduction v Reference
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	
Method	Mixed model for repeated measure
Parameter estimate	Least square mean difference
Point estimate	0.1062
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0485
upper limit	0.2609

Secondary: Change from baseline in standardised asthma quality of life questionnaire for 12 years and older (AQLQ(S)+12) at the end of the reduction

period	
End point title	Change from baseline in standardised asthma quality of life questionnaire for 12 years and older (AQLQ(S)+12) at the end of the reduction period

End point description:

The AQLQ(S)+12 is a Patient-Reported Outcome (PRO) that measures the health-related quality of life experienced by asthma patients. The questionnaire comprises 4 separate domains (symptoms, activity limitations, emotional function, and environmental stimuli). Patients are asked to recall their experiences during the previous 2 weeks before each visit and to score each of the questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The statistical test is mixed model for repeated measure (MMRM) with fixed effects for treatment arm, visit, baseline value, and treatment-by-visit interaction with an unstructured covariance structure. The FAS population included for this endpoint, all randomised patients, irrespective of their protocol adherence and continued participation in the study.

End point type	Secondary

End point timeframe:

Week 0 (baseline) and at Week 32

End point values	Treatment reduction	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	35		
Units: Change from baseline in score				
least squares mean (standard error)	-0.0279 (± 0.0559)	0.0064 (± 0.0950)		

Statistical analyses

Statistical analysis title	Comparison with reference arm

Statistical analysis description:

Comparison with reference arm

Comparison groups	Treatment reduction v Reference
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	
Method	Mixed model for repeated measure
Parameter estimate	Least square mean difference
Point estimate	-0.0343
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2527
upper limit	0.1841

Secondary: Number of patients with no deterioration in AQLQ(S)+12 at the end of the reduction period	
End point title	Number of patients with no deterioration in AQLQ(S)+12 at the

	end of the reduction period

End point description:

The AQLQ(S)+12 is a PRO that measures the health-related quality of life experienced by asthma patients. The questionnaire comprises 4 separate domains (symptoms, activity limitations, emotional function, and environmental stimuli). Patients are asked to recall their experiences during the previous 2 weeks before each visit and to score each of the questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). AQLQ(S)+12 deterioration was defined as at least a 0.5 unit decrease in AQLQ(S)+12 total score from baseline. Patients with no deterioration include patients with improvement or no change. The FAS population included for this endpoint, all randomised patients, irrespective of their protocol adherence and continued participation in the study.

End point type	Secondary

End point timeframe:

At Week 32

End point values	Treatment reduction	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	43		
Units: Participants				
Improvement	12	3		
No change	73	28		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with no deterioration in ACQ-5 at the end of the reduction period

End point title	Number of patients with no deterioration in ACQ-5 at the end of the reduction period

End point description:

Change from baseline in the ACQ-5 patient reported outcome. This instrument contains 5 asthma symptom questions, rated from 0 (total control) to 6 (severely uncontrolled). The ACQ-5 score is the mean of the responses. Mean scores ≤0.75 indicating well controlled, >0.75 and <1.5 indicate partly controlled and ≥1.5 indicate not well controlled asthma. ACQ-5 deterioration is defined as at least a 0.5 unit increase in ACQ-5 score from baseline. Patients with no deterioration include patients with improvement or no change. The FAS population included for this endpoint, all randomised patients, irrespective of their protocol adherence and continued participation in the study.

End point type	Secondary

End point timeframe:

At Week 32

End point values	Treatment reduction	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	43		
Units: Participants				
Improvement	6	2		
No change	87	28		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in pre-bronchodilator forced expiratory volume in 1 second (FEV1) during the study period

End point title	Change from baseline in pre-bronchodilator forced expiratory volume in 1 second (FEV1) during the study period

End point description:

The potential for benralizumab-treated patients to maintain lung function while stepping down Symbicort® maintenance treatment was assessed. The FEV1 is the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration, expressed in liters. Change from baseline pre-bronchodilator FEV1 calculated as post-baseline pre-bronchodilator FEV1 (L) minus baseline pre-bronchodilator FEV1 (L) for all post-baseline measurement points. The FAS population included for this endpoint, all randomised patients, irrespective of their protocol adherence and continued participation in the study. Here, "n" represents the number of patients analyzed for each row of this endpoint.

End point type	Secondary

End point timeframe:

At Week 0 (baseline), and at Weeks 8, 16, 24, 32, 40, and 48

End point values	Treatment reduction	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	43		
Units: Liter				
least squares mean (standard error)				
Week 8 (n= 102; 33)	0.0411 (± 0.0183)	0.0549 (± 0.0315)		
Week 16 (n= 97; 34)	0.0299 (± 0.0215)	0.0115 (± 0.0363)		
Week 24 (n= 92; 31)	-0.0536 (± 0.0317)	0.0644 (± 0.0540)		
Week 32 (n= 89; 31)	-0.0824 (± 0.0285)	-0.0016 (± 0.0482)		
Week 40 (n= 93; 32)	-0.0953 (± 0.0280)	0.0428 (± 0.0476)		
Week 48 (n= 92; 29)	-0.0889 (± 0.0272)	0.0059 (± 0.0475)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised asthma exacerbation rate during the study period

End point title	Annualised asthma exacerbation rate during the study period

End point description:

Asthma exacerbation rate was assessed. An asthma exacerbation was defined as a worsening of asthma symptoms that led to any of the following: a) Temporary bolus/burst of systemic corticosteroids (≥3 consecutive days); b) Single depo-injectable dose of corticosteroids (equivalent to a 3-day bolus/burst); c) Visit to emergency room/urgent care (treatment <24 hours) requiring systemic corticosteroids; d) Hospitalization (admission/evaluation ≥24 hours) due to asthma. The FAS population included for this endpoint, all randomised patients, irrespective of their protocol adherence and continued participation in the study.

End point type	Secondary

End point timeframe:

From Week 0 up to Week 48

End point values	Treatment reduction	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	43		
Units: Rate				
number (confidence interval 95%)	0.14 (0.09 to 0.23)	0.14 (0.06 to 0.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative total daily inhaled corticosteroids (ICS) dose, by period

End point title	Cumulative total daily inhaled corticosteroids (ICS) dose, by period

End point description:

The cumulative total daily ICS dose (maintenance +reliever) for: a) reduction period; b) maintenance period; c) study period was assessed. The FAS population included for this endpoint, all randomised patients, irrespective of their protocol adherence and continued participation in the study. Here, "n" represents the number of patients analyzed for each row of this endpoint.

End point type	Secondary

End point timeframe:

Reduction period (From Week 0 up to Week 32); maintenance period (From Week 32 up to Week 48); Study period (Week 0 up to end of maintenance period/ end of study)

End point values	Treatment reduction	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	42		
Units: Microgram				
arithmetic mean (standard deviation)				
Reduction period (n= 125; 42)	115956.8 (± 73223.93)	312857.1 (± 81251.22)		
Maintenance period (n= 102; 38)	50984.3 (± 51148.59)	150400.0 (± 42180.46)		
Study period (n= 125; 42)	157560.0 (± 114123.69)	448933.3 (± 131247.22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total daily ICS dose (maintenance + reliever) at the end of the reduction period

End point title	Total daily ICS dose (maintenance + reliever) at the end of the reduction period

End point description:

The mean total daily ICS dose (maintenance + reliever) during the 8 weeks prior to end of the reduction period was assessed. The FAS population included for this endpoint, all randomised patients, irrespective of their protocol adherence and continued participation in the study.

End point type	Secondary

End point timeframe:

At Week 32

End point values	Treatment reduction	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	39		
Units: Microgram				
arithmetic mean (standard deviation)	380.028 (± 440.4995)	1401.796 (± 316.9718)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of participants using the same Symbicort® daily dose at the end of the maintenance period (Week 48) that they achieved at the end of the reduction period (Week 32)

End point title	Proportion of participants using the same Symbicort® daily dose at the end of the maintenance period (Week 48) that they achieved at the end of the reduction period (Week 32)[3]

End point description:

Proportion of patients using the same Symbicort daily dose at the end of the maintenance period that they achieved at the end of the reduction period. Proportions were based on patients with non-missing Week 32 and Week 48 Symbicort doses. The FAS population included for this endpoint, all randomised patients, irrespective of their protocol adherence and continued participation in the study.

End point type	Secondary

End point timeframe:

At Week 48

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was performed.

End point values	Treatment reduction			
Subject group type	Reporting group			
Number of subjects analysed	118			
Units: Proportion				
number (confidence interval 95%)	0.958 (0.9039 to 0.9861)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with at least 1 exacerbation occurring from end of the reduction period to end of the maintenance period

End point title	Number of patients with at least 1 exacerbation occurring from end of the reduction period to end of the maintenance period

End point description:

Number of patients with at least 1 exacerbation occurring from end of the reduction period to end of the maintenance period. The FAS population included for this endpoint, all randomised patients, irrespective of their protocol adherence and continued participation in the study.

End point type	Secondary

End point timeframe:

From Week 32 to Week 48

End point values	Treatment reduction	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	43		
Units: Participants	5	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Total daily ICS dose from the end of the reduction period to the end of the maintenance period

End point title	Total daily ICS dose from the end of the reduction period to the end of the maintenance period

End point description:

Total daily ICS dose from the end of the reduction period to the end of the maintenance period. The FAS population included for this endpoint, all randomised patients, irrespective of their protocol adherence and continued participation in the study. Here, "n" represents the number of patients analyzed for each row of this endpoint.

End point type	Secondary

End point timeframe:

Week 32, Week 40, and Week 48

End point values	Treatment reduction	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	38		
Units: Microgram				
arithmetic mean (standard deviation)				
Week 32 (n= 119; 38)	383.221 (± 440.9649)	1438.685 (± 220.6355)		
Week 40 (n= 119; 38)	408.458 (± 475.6986)	1424.624 (± 321.5752)		
Week 48 (n= 117; 38)	376.356 (± 449.6614)	1265.356 (± 472.5244)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in ACQ-5 from the end of the reduction period to the end of the maintenance period

End point title	Change in ACQ-5 from the end of the reduction period to the end of the maintenance period

End point description:

Change in ACQ-5 score from end of reduction to end of maintenance is reported. The FAS population included for this endpoint, all randomised patients, irrespective of their protocol adherence and continued participation in the study.

End point type	Secondary

End point timeframe:

From Week 32 to Week 48

End point values	Treatment reduction	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	34		
Units: Change in score				
arithmetic mean (standard deviation)	-0.07 (± 0.575)	-0.20 (± 0.814)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in AQLQ(S)+12 from the end of the reduction period to the end of the maintenance period

End point title	Change in AQLQ(S)+12 from the end of the reduction period to the end of the maintenance period

End point description:

Change in AQLQ(S)+12 from the end of the reduction period to the end of the maintenance period is reported. The FAS population included for this endpoint, all randomised patients, irrespective of their protocol adherence and continued participation in the study.

End point type	Secondary

End point timeframe:

From Week 32 to Week 48

End point values	Treatment reduction	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	31		
Units: Change in score				
arithmetic mean (standard deviation)	-0.008 (± 0.4720)	0.060 (± 0.5658)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in FEV1 from the end of the reduction period to the end of the maintenance period

End point title	Change in FEV1 from the end of the reduction period to the end of the maintenance period

End point description:

The change from the end of the reduction period to the end of the maintenance period for pre-bronchodilator Forced Expiratory Volume in 1 second (FEV1) was calculated as Week 48 pre-bronchodilator FEV1 (Liter [L]) minus the maintenance period baseline pre-bronchodilator FEV1 (L). The FEV1 is the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration, expressed in liters. The FAS population included for this endpoint, all randomised patients, irrespective of their protocol adherence and continued participation in the study.

End point type	Secondary

End point timeframe:

From Week 32 to Week 48

End point values	Treatment reduction	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	30		
Units: Liter				
arithmetic mean (standard deviation)	0.0089 (± 0.2320)	0.0040 (± 0.2264)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients that met each composite endpoint defining clinical remission

End point title	Number of patients that met each composite endpoint defining clinical remission

End point description:

Clinical remission in patients at end of the reduction and maintenance periods was assessed. A remission score, based on the number of remission criteria achieved at week 32 or week 48, was calculated for patients who met 0, 1, 2, and all 3 remission criteria (zero exacerbations, ACQ-5 < 1.5, or ACQ-5 <= 0.75, < 10% FEV1 deterioration). The FAS population included for this endpoint, all randomised patients, irrespective of their protocol adherence and continued participation in the study. Here, "n" represents the number of patients analyzed for each row of this endpoint.

End point type	Secondary

End point timeframe:

At Week 32 and Week 48

End point values	Treatment reduction	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	38		
Units: Participants				
No asthma exacerbation at Week 32 (n= 119; 38)	108	37		
No asthma exacerbation at Week 48 (n= 117; 37)	101	32		
ACQ-5 <1.5 at Week 32 (n= 115; 35)	106	32		
ACQ-5 <1.5 at Week 48 (n= 113; 35)	103	32		
ACQ-5 ≤ 0.75 at Week 32 (n= 115; 35)	65	21		
ACQ-5 ≤ 0.75 at Week 48 (n= 113; 35)	68	21		
FEV1<10% decrease at Week 32 (n= 89; 31)	59	26		
FEV1 < 10% decrease at Week 48 (n= 92; 29)	66	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients that met 0, 1, 2, and all 3 composite remission endpoints

End point title	Number of patients that met 0, 1, 2, and all 3 composite remission endpoints

End point description:

Clinical remission in patients at end of the reduction and maintenance periods was assessed. A remission score, based on the number of remission criteria achieved at week 32 or week 48, was calculated for patients who met 0, 1, 2, and all 3 remission criteria (zero exacerbations, ACQ-5 < 1.5, or ACQ-5 <= 0.75, < 10% FEV1 deterioration). The FAS population included for this endpoint, all randomised patients, irrespective of their protocol adherence and continued participation in the study. Here, #1a is defined as zero exacerbation, ACQ-5 ≤ 0.75, FEV1 < 10% decrease from baseline, and #1b as zero exacerbation, ACQ-5 < 1.5, FEV1 < 10% decrease from baseline. Also "n" represents the number of patients analyzed for each row of this endpoint.

End point type	Secondary

End point timeframe:

At Week 32 and Week 48

End point values	Treatment reduction	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	28		
Units: Participants				
Remission score (0) #1a at week 32 (n= 86; 28)	2	0		
Remission score (1) #1a at week 32 (n= 86; 28)	15	5		
Remission score (2) #1a at week 32 (n= 86; 28)	40	8		
Remission score (3) #1a at week 32 (n= 86; 28)	29	15		
Remission score (0) #1a at week 48 (n= 89; 28)	1	1		
Remission score (1) #1a at week 48 (n= 89; 28)	15	4		
Remission score (2) #1a at week 48 (n= 89; 28)	41	9		
Remission score (3) #1a at week 48 (n= 89; 28)	32	14		
Remission score (0) #1b at week 32 (n= 86; 28)	1	0		
Remission score (1) #1b at week 32 (n= 86; 28)	5	2		
Remission score (2) #1b at week 32 (n= 86; 28)	32	5		

Remission score (3) #1b at week 32 (n= 86; 28)	48	21		
Remission score (0) #1b at week 48 (n= 89; 28)	0	0		
Remission score (1) #1b at week 48 (n= 89; 28)	5	2		
Remission score (2) #1b at week 48 (n= 89; 28)	36	7		
Remission score (3) #1b at week 48 (n= 89; 28)	48	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with adverse events or serious adverse events

End point title	Number of patients with adverse events or serious adverse events

End point description:

The safety and tolerability of benralizumab in patients with severe asthma, while stepping down Symbicort® maintenance treatment and maintaining asthma symptom control was assessed. The safety analysis set (SAF) included for this endpoint, all patients from the FAS who receive any amount of study treatment and will be used for all safety analyses.

End point type	Secondary

End point timeframe:

From Week 0 (randomization) to Week 48 or end of treatment (total period of study is 2.5 years)

End point values	Treatment reduction	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	42		
Units: Participants				
Any adverse event (AE)	91	35		
Any AE with outcome = death	0	0		
Serious adverse events, including deaths.	12	5		
Any AE leading to discontinuation of benralizumab	3	1		
Any AE leading to discontinuation of Symbicort	3	1		
Any AE leading to discontinuation of Ventolin	2	1		
Any AE leading to withdrawal from study	3	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Week 0 (randomization) to Week 48 or end of treatment (total period of study is 2.5 years)

Adverse event reporting additional description:

The safety analysis set (SAF) included all patients from the FAS who receive any amount of study treatment and will be used for all safety analyses.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Reference

Reporting group description:

Patients received benralizumab 30 mg Q8W + high-dose Symbicort® 400/12 µg maintenance × 2 inhalations BID + Ventolin® (salbutamol 100 µg) reliever PRN therapy. Eligible patients randomised to the reference arm continued on high-dose Symbicort® maintenance treatment and Ventolin® reliever treatment.

Reporting group title	Treatment reduction

Reporting group description:

Patients received benralizumab 30 mg every 8 weeks (Q8W) during the study period, and high-dose Symbicort maintenance 400/12 µg ×2 inhalations BID + Ventolin (salbutamol 100 µg) reliever as needed (PRN), tapering to, medium-dose Symbicort 200/6 µg ×2 inhalations BID maintenance + Symbicort 200/6 µg reliever PRN, low dose Symbicort 200/6 µg x 1 inhalation BID maintenance + Symbicort 200/6 µg reliever PRN; or Symbicort 200/6 µg reliever only, as per tapering scheme and depending on the degree of asthma control). The reduction period in this arm lasted for 32 weeks.

Serious adverse events	Reference	Treatment reduction	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 42 (11.90%)	12 / 125 (9.60%)	
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)			
Gallbladder adenocarcinoma			
subjects affected / exposed	0 / 42 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 42 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal compression fracture			
subjects affected / exposed	0 / 42 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaccination complication			
subjects affected / exposed	1 / 42 (2.38%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 42 (2.38%)	0 / 125 (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			
Seizure			
subjects affected / exposed	0 / 42 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Eosinophilic granulomatosis with polyangiitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 125 (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			
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 42 (0.00%)	1 / 125 (0.80%)	
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 / 42 (2.38%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 42 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Helicobacter infection			
subjects affected / exposed	1 / 42 (2.38%)	0 / 125 (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	0 / 42 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 42 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital abscess			
subjects affected / exposed	0 / 42 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 42 (0.00%)	1 / 125 (0.80%)	
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: 5 %

Non-serious adverse events	Reference	Treatment reduction	
Total subjects affected by non-serious adverse events subjects affected / exposed	20 / 42 (47.62%)	46 / 125 (36.80%)	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	4 / 42 (9.52%)	17 / 125 (13.60%)	
occurrences (all)	4	20	
Infections and infestations			
COVID-19			
subjects affected / exposed	9 / 42 (21.43%)	19 / 125 (15.20%)	
occurrences (all)	9	19	
Bronchitis			
subjects affected / exposed	1 / 42 (2.38%)	7 / 125 (5.60%)	
occurrences (all)	1	8	
Rhinitis			
subjects affected / exposed	3 / 42 (7.14%)	1 / 125 (0.80%)	
occurrences (all)	4	1	
Nasopharyngitis			
subjects affected / exposed	7 / 42 (16.67%)	10 / 125 (8.00%)	
occurrences (all)	8	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2020	Amendment 1 Version 2.0: Removal of nasosorption sampling and addition of SARS-CoV-2 test and induced sputum sampling; study mitigation during study disruptions due to cases of civil crisis, natural disaster, or public health crisis which will provide sites with measures that may be implemented if a patient is not able to visit a study site to ensure that the clinical trial can continue whilst minimizing risk to the patient, maintaining compliance with Good Clinical Practice, and minimizing risks to the study integrity.
17 September 2021	Amendment 2 Version 3.0: Updated the estimated date of last patient completed; Added new criteria to include details about patients who received COVID-19 vaccination; New section was added to explain restrictions related to blood donation; Added new row to study treatment table to include conversion of 200/6 and 400/12 Symbicort into 'total' µg; Added wording about home completion of COVID- 19 related electronic patient reported outcome; Added new population for analysis-Safety Analysis. set
15 November 2022	Amendment 3 Version 4.0: Updated to add a secondary endpoint ie, clinical remission; Deleted reference to analysis after patients reach V6 (32 weeks).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported