



## Clinical trial results:

### **A Multicentre, Randomised, Double-blind, Parallel Group, Placebo-controlled, Phase 3b Study to Evaluate the Potential Effect of Benralizumab on the Humoral Immune Response to the Seasonal Influenza Vaccination in Adolescent and Young Adult Patients with Severe Asthma (ALIZE)**

#### **Summary**

EudraCT number	2016-001717-24
Trial protocol	Outside EU/EEA
Global end of trial date	24 January 2017

#### **Results information**

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017

#### **Trial information**

##### **Trial identification**

Sponsor protocol code	D3250C00033
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##### **Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02814643
WHO universal trial number (UTN)	-

Notes:

#### **Sponsors**

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	151 85, Södertälje, Sweden,
Public contact	Mitchell Goldman MD, PhD, AstraZeneca, +1 610 457 5585, Mitchell.Goldman@astrazeneca.com
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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	24 August 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 January 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to evaluate the potential effect of benralizumab on the humoral immune response following seasonal influenza virus vaccination in adolescent and young adult patients with severe asthma.

Protection of trial subjects:

No committees were used for this study. Patients were free to withdraw from the study medication or study assessments at any time without prejudice to further treatment.

Background therapy:

Background asthma medications were to be maintained at stable doses from Visit 1 until the end of the study. If changing the inhaled corticosteroid or long-acting beta2-agonist dose or any other controller medication was judged as necessary by the Investigator or the patient's healthcare provider, the justification was to have been documented in the source and the change in doses was to have been reflected in the electronic case report form.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	01 July 2016
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	United States: 103
Worldwide total number of subjects	103
EEA total number of subjects	0

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	72

Adults (18-64 years)	31
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This trial was conducted at 30 trial centres in the United States between 01 July 2016 and 24 January 2017.

### Pre-assignment

Screening details:

The trial duration was up to 23 weeks, consisting of an initial screening period lasting up to 3 weeks, a 12-week treatment period, and a follow-up visit 8 weeks after the last dose of study drug.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Placebo solution was visually matched with benralizumab solution. As patients on active benralizumab treatment were expected to have lower blood eosinophil counts than patients on placebo, monocyte counts were redacted from central laboratory reports to prevent the Investigator from deducing the patient's study treatment, and centre staff who were directly involved in the patient's management were to remain blinded to any eosinophil, basophil, and monocyte results.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Benralizumab 30mg

Arm description:

Benralizumab 30mg/day subcutaneous

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/mL solution for injection in accessorised pre-filled syringe, 1 mL fill volume, given every 4 weeks for 3 doses.

Investigational medicinal product name	Influenza vaccine
Investigational medicinal product code	
Other name	Flulaval Quadrivalent
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

60 mcg hemagglutinin per 0.5 mL dose (15 mcg each of 4 influenza viral strains), given once at Week 8

<b>Arm title</b>	Placebo
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Arm description:

Placebo to benralizumab subcutaneous

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

Dosage and administration details:

Matching placebo solution for injection in accessorised pre-filled syringe, 1 mL fill volume, given every 4 weeks for 3 doses.

Investigational medicinal product name	Influenza vaccine
Investigational medicinal product code	
Other name	Flulaval Quadrivalent
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

60 mcg hemagglutinin per 0.5 mL dose (15 mcg each of 4 influenza viral strains), given once at Week 8

<b>Number of subjects in period 1</b>	Benralizumab 30mg	Placebo
Started	51	52
Completed	50	49
Not completed	1	3
Consent withdrawn by subject	1	2
Lost to follow-up	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Benralizumab 30mg
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Reporting group description:

Benralizumab 30mg/day subcutaneous

Reporting group title	Placebo
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Reporting group description:

Placebo to benralizumab subcutaneous

Reporting group values	Benralizumab 30mg	Placebo	Total
Number of subjects	51	52	103
Age Categorical Units: Subjects			
≥12 to ≤17 years	36	36	72
≥18 to ≤21 years	15	16	31
Age Continuous Units: years			
arithmetic mean	16	15.7	
standard deviation	± 2.65	± 2.99	-
Gender, Male/Female Units: Subjects			
Female	21	21	42
Male	30	31	61
Race, Customised Units: Subjects			
American Indian Or Alaska Native	0	1	1
Black Or African American	13	13	26
Other	0	2	2
White	38	36	74

## End points

### End points reporting groups

Reporting group title	Benralizumab 30mg
Reporting group description:	Benralizumab 30mg/day subcutaneous
Reporting group title	Placebo
Reporting group description:	Placebo to benralizumab subcutaneous

### Primary: Postdose strain-specific hemagglutination-inhibition (HAI) antibody geometric mean fold rise from Week 8 to Week 12

End point title	Postdose strain-specific hemagglutination-inhibition (HAI) antibody geometric mean fold rise from Week 8 to Week 12
End point description:	To compare the geometric mean fold rises in influenza strain-specific hemagglutination-inhibition responses from Week 8 to Week 12 between patients receiving benralizumab 30mg and patients receiving placebo.
End point type	Primary
End point timeframe:	4 weeks

End point values	Benralizumab 30mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	49		
Units: Geometric mean fold rise				
least squares mean (standard error)				
Influenza A H1N1	3.6 (± 1.22)	3.13 (± 1.22)		
Influenza A H3N2	3.25 (± 1.18)	3.85 (± 1.18)		
Influenza B Yamagata lineage	3.42 (± 1.16)	3.17 (± 1.16)		
Influenza B Victoria lineage	4.08 (± 1.19)	3.27 (± 1.19)		

### Statistical analyses

Statistical analysis title	Influenza A H1N1
Comparison groups	Benralizumab 30mg v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	
Method	ANCOVA
Parameter estimate	Geometric least-square mean ratio
Point estimate	0.87

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.56
upper limit	1.35

<b>Statistical analysis title</b>	Influenza A H3N2
Comparison groups	Benralizumab 30mg v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	
Method	ANCOVA
Parameter estimate	Geometric least-square mean ratio
Point estimate	1.19
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.82
upper limit	1.71

<b>Statistical analysis title</b>	Influenza B Yamagata lineage
Comparison groups	Benralizumab 30mg v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	
Method	ANCOVA
Parameter estimate	Geometric least-square mean ratio
Point estimate	0.93
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.67
upper limit	1.29

<b>Statistical analysis title</b>	Influenza B Victoria lineage
Comparison groups	Benralizumab 30mg v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	
Method	ANCOVA
Parameter estimate	Geometric least-square mean ratio
Point estimate	0.8



Confidence interval	
level	90 %
sides	2-sided
lower limit	0.54
upper limit	1.19

**Primary: Postdose strain-specific hemagglutination-inhibition antibody geometric mean titers obtained at Week 12**

End point title	Postdose strain-specific hemagglutination-inhibition antibody geometric mean titers obtained at Week 12
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End point description:

To compare the geometric mean titers of hemagglutination-inhibition antibody as a measure of influenza strain-specific response at Week 12 between patients receiving benralizumab 30mg and patients receiving placebo.

End point type	Primary
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End point timeframe:

12 weeks

End point values	Benralizumab 30mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	49		
Units: Geometric mean titer				
least squares mean (standard error)				
Influenza A H1N1	521.06 (± 1.13)	518.6 (± 1.13)		
Influenza A H3N2	170.73 (± 1.15)	219.35 (± 1.15)		
Influenza B Yamagata lineage	61.47 (± 1.13)	63.15 (± 1.13)		
Influenza B Victoria lineage	53.1 (± 1.14)	66.85 (± 1.14)		

**Statistical analyses**

Statistical analysis title	Influenza A H1N1
Comparison groups	Benralizumab 30mg v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	
Method	ANCOVA
Parameter estimate	Geometric least-square mean ratio
Point estimate	1
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.76
upper limit	1.31

<b>Statistical analysis title</b>	Influenza A H3N2
Comparison groups	Benralizumab 30mg v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	
Method	ANCOVA
Parameter estimate	Geometric least-square mean ratio
Point estimate	1.28
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.93
upper limit	1.77

<b>Statistical analysis title</b>	Influenza B Yamagata lineage
Comparison groups	Benralizumab 30mg v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	
Method	ANCOVA
Parameter estimate	Geometric least-square mean ratio
Point estimate	1.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.79
upper limit	1.34

<b>Statistical analysis title</b>	Influenza B Victoria lineage
Comparison groups	Benralizumab 30mg v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	
Method	ANCOVA
Parameter estimate	Geometric least-square mean ratio
Point estimate	1.26
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.93
upper limit	1.7

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**Primary: Proportion of patients who experienced a strain-specific postdose antibody response at Week 12 with antibody response defined as a  $\geq 4$ -fold rise in hemagglutination-inhibition antibody titer from Week 8 to Week 12**

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End point title	Proportion of patients who experienced a strain-specific postdose antibody response at Week 12 with antibody response defined as a $\geq 4$ -fold rise in hemagglutination-inhibition antibody titer from Week 8 to Week 12 <sup>[1]</sup>
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End point description:

To compare the proportions of patients experiencing influenza strain-specific responses as measured by  $\geq 4$ -fold rises in hemagglutination-inhibition antibody titer from Week 8 to Week 12 between patients receiving benralizumab 30mg and patients receiving placebo.

End point type	Primary
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End point timeframe:

4 weeks

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 analyses

End point values	Benralizumab 30mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	49		
Units: Proportion of patients				
number (confidence interval 90%)				
Influenza A H1N1	0.44 (0.32 to 0.57)	0.306 (0.2 to 0.43)		
Influenza A H3N2	0.5 (0.38 to 0.62)	0.49 (0.37 to 0.62)		
Influenza B Yamagata lineage	0.48 (0.36 to 0.6)	0.49 (0.37 to 0.62)		
Influenza B Victoria lineage	0.56 (0.43 to 0.68)	0.408 (0.29 to 0.54)		

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**Statistical analyses**

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No statistical analyses for this end point

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**Primary: Proportion of patients who achieved a strain-specific postdose hemagglutination-inhibition antibody titer  $\geq 40$  at Week 12**

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End point title	Proportion of patients who achieved a strain-specific postdose hemagglutination-inhibition antibody titer $\geq 40$ at Week 12 <sup>[2]</sup>
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End point description:

To compare the proportions of patients experiencing influenza strain-specific responses as measured by  $\geq 40$ -fold rises in hemagglutination-inhibition antibody titer at Week 12 between patients receiving benralizumab 30mg and patients receiving placebo.

End point type	Primary
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End point timeframe:

12 weeks

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: No statistical analyses

End point values	Benralizumab 30mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	49		
Units: Proportion of patients				
number (confidence interval 90%)				
Influenza A H1N1	1 (0.94 to 1)	1 (0.94 to 1)		
Influenza A H3N2	0.98 (0.91 to 1)	0.98 (0.91 to 1)		
Influenza B Yamagata lineage	0.86 (0.75 to 0.93)	0.796 (0.68 to 0.88)		
Influenza B Victoria lineage	0.78 (0.66 to 0.87)	0.878 (0.77 to 0.95)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of patients who achieved a strain-specific postdose hemagglutination inhibition antibody titre $\geq 320$ at Week 12

End point title	Proportion of patients who achieved a strain-specific postdose hemagglutination inhibition antibody titre $\geq 320$ at Week 12
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End point description:

To compare the proportions of patients experiencing influenza strain-specific responses as measured by  $\geq 320$ -fold rises in hemagglutination-inhibition antibody titer at Week 12 between patients receiving benralizumab 30mg and patients receiving placebo.

End point type	Secondary
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End point timeframe:

12 weeks

End point values	Benralizumab 30mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	49		
Units: Proportion of patients				
number (confidence interval 90%)				
Influenza A H1N1	0.84 (0.73 to 0.92)	0.857 (0.75 to 0.93)		
Influenza A H3N2	0.5 (0.38 to 0.62)	0.612 (0.48 to 0.73)		
Influenza B Yamagata lineage	0.02 (0 to 0.09)	0.02 (0 to 0.09)		
Influenza B Victoria lineage	0.08 (0.03 to 0.17)	0.041 (0.01 to 0.12)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Postdose strain-specific microneutralisation antibody geometric mean fold rise from Week 8 to Week 12

End point title	Postdose strain-specific microneutralisation antibody geometric mean fold rise from Week 8 to Week 12
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End point description:

To compare the geometric mean fold rises in influenza strain-specific microneutralization antibody responses from Week 8 to Week 12 between patients receiving benralizumab 30mg and patients receiving placebo.

End point type	Secondary
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End point timeframe:

4 weeks

End point values	Benralizumab 30mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	49		
Units: Geometric mean fold rise				
geometric mean (geometric coefficient of variation)				
Influenza A H1N1	5.1 (± 521.4)	4.4 (± 329.4)		
Influenza A H3N2	3.2 (± 149.8)	3.6 (± 210)		
Influenza B Yamagata lineage	2.8 (± 148.9)	3.2 (± 141.3)		
Influenza B Victoria lineage	3.8 (± 224.1)	3.5 (± 195.3)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Postdose strain-specific serum microneutralization antibody geometric mean titers obtained at Week 12

End point title	Postdose strain-specific serum microneutralization antibody geometric mean titers obtained at Week 12
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End point description:

To compare the geometric mean titers of microneutralization antibody as a measure of influenza strain-specific response at Week 12 between patients receiving benralizumab 30mg and patients receiving placebo.

End point type	Secondary
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End point timeframe:

12 weeks

End point values	Benralizumab 30mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	49		
Units: Geometric mean titer				
geometric mean (geometric coefficient of variation)				
Influenza A H1N1	3774.1 (± 181.7)	3969.1 (± 154)		
Influenza A H3N2	4307.5 (± 169)	4351.3 (± 171)		
Influenza B Yamagata lineage	350.2 (± 103.6)	336.2 (± 114.3)		
Influenza B Victoria lineage	164.5 (± 178.5)	234.4 (± 135)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of patients who experience a strain-specific postdose antibody response at Week 12 with antibody response defined as a ≥4-fold rise in microneutralization antibody titer from Week 8 to Week 12

End point title	Proportion of patients who experience a strain-specific postdose antibody response at Week 12 with antibody response defined as a ≥4-fold rise in microneutralization antibody titer from Week 8 to Week 12
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End point description:

To compare the proportions of patients experiencing influenza strain-specific responses as measured by ≥4-fold rises in microneutralization antibody titer from Week 8 to Week 12 between patients receiving benralizumab 30mg and patients receiving placebo.

End point type	Secondary
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End point timeframe:

4 weeks

End point values	Benralizumab 30mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	49		
Units: Proportion of patients				
number (confidence interval 90%)				
Influenza A H1N1	0.42 (0.3 to 0.55)	0.408 (0.29 to 0.54)		
Influenza A H3N2	0.44 (0.32 to 0.57)	0.429 (0.31 to 0.56)		
Influenza B Yamagata lineage	0.28 (0.18 to 0.4)	0.388 (0.27 to 0.52)		
Influenza B Victoria lineage	0.4 (0.28 to 0.53)	0.388 (0.27 to 0.52)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in mean Asthma Control Questionnaire score at Week 12

End point title	Change from baseline in mean Asthma Control Questionnaire score at Week 12
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End point description:

To compare the change from baseline at Week 12 in mean Asthma Control Questionnaire score between patients receiving benralizumab 30mg and patients receiving placebo.

End point type	Secondary
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End point timeframe:

12 weeks

End point values	Benralizumab 30mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	49		
Units: Difference in score				
arithmetic mean (standard deviation)	-0.5 ( $\pm$ 1.114)	-0.42 ( $\pm$ 0.925)		

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All adverse events, including serious adverse events, were collected from the time the patient, parent, or legal guardian signed the informed consent/assent throughout the treatment period and including the follow-up period (through Week 20).

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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### Reporting groups

Reporting group title	Benralizumab 30mg
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Reporting group description:

Benralizumab 30mg/day subcutaneous

Reporting group title	Placebo
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Reporting group description:

Placebo to benralizumab subcutaneous

Serious adverse events	Benralizumab 30mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 51 (0.00%)	2 / 52 (3.85%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	
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 %



<b>Non-serious adverse events</b>	Benralizumab 30mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 51 (27.45%)	18 / 52 (34.62%)	
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	2 / 51 (3.92%)	0 / 52 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 51 (3.92%)	4 / 52 (7.69%)	
occurrences (all)	3	4	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 51 (3.92%)	0 / 52 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	1 / 51 (1.96%)	2 / 52 (3.85%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 51 (5.88%)	3 / 52 (5.77%)	
occurrences (all)	5	3	
Cough			
subjects affected / exposed	0 / 51 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Oropharyngeal pain			
subjects affected / exposed	3 / 51 (5.88%)	2 / 52 (3.85%)	
occurrences (all)	4	2	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 51 (1.96%)	2 / 52 (3.85%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue disorders			
Costochondritis			
subjects affected / exposed	2 / 51 (3.92%)	0 / 52 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			

Gastroenteritis viral			
subjects affected / exposed	3 / 51 (5.88%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Nasopharyngitis			
subjects affected / exposed	2 / 51 (3.92%)	4 / 52 (7.69%)	
occurrences (all)	2	5	
Sinusitis			
subjects affected / exposed	2 / 51 (3.92%)	1 / 52 (1.92%)	
occurrences (all)	2	1	
Upper respiratory tract infection			
subjects affected / exposed	3 / 51 (5.88%)	1 / 52 (1.92%)	
occurrences (all)	4	1	
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 51 (3.92%)	0 / 52 (0.00%)	
occurrences (all)	2	0	

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported