Clinical trial results:
A Multicentre, Double-blind, Randomized, Parallel Group, Phase 3 Safety Extension Study to Evaluate the Safety and Tolerability of Benralizumab (MEDI-563) in Asthmatic Adults and Adolescents on Inhaled Corticosteroid Plus Long-acting 2 Agonist (BORA)

Summary

EudraCT number	2014-001086-27
Trial protocol	GB CZ PL DE SE BG ES FR
Global end of trial date	14 August 2018

Results information

Result version number	v1
This version publication date	27 December 2018
First version publication date	27 December 2018

Trial information

Trial identification

Sponsor protocol code	D3250C00021

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02258542
WHO universal trial number (UTN)	U1111-1162-2422

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Vastra Malarehamnen 9, Sodertalje, Sweden, 151 85
Public contact	Ubaldo Martin, Global Clinical Lead Benralizumab, AstraZeneca AB, Ubaldo.Martin@astrazeneca.com
Scientific contact	AZ Clinical Study Information, AstraZeneca AB, 46 855 326000, 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	Interim
Date of interim/final analysis	31 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 October 2017
Global end of trial reached?	Yes
Global end of trial date	14 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To assess the safety and tolerability of 2 dosing regimens of benralizumab for adult patients during the 56-week treatment period and through the follow-up period (16 weeks from day of last dose) 2. To assess the safety and tolerability of 2 dosing regimens of benralizumab for adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)

Protection of trial subjects:

Data safety monitoring board (DSMB) evaluates cumulative safety and other clinical trial data at regular intervals and making appropriate recommendations based on the available data. The DSMB functions independently of all other individuals associated with the conduct of the studies, including the study sponsor, AstraZeneca. The committee operates in accordance with a DSMB charter.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 220
Country: Number of subjects enrolled	Australia: 36
Country: Number of subjects enrolled	Brazil: 31
Country: Number of subjects enrolled	Bulgaria: 93
Country: Number of subjects enrolled	Canada: 74
Country: Number of subjects enrolled	Chile: 30
Country: Number of subjects enrolled	Czech Republic: 42
Country: Number of subjects enrolled	France: 83
Country: Number of subjects enrolled	Germany: 178
Country: Number of subjects enrolled	Japan: 73
Country: Number of subjects enrolled	Peru: 50
Country: Number of subjects enrolled	Philippines: 60
Country: Number of subjects enrolled	Poland: 355
Country: Number of subjects enrolled	Romania: 41
Country: Number of subjects enrolled	Russian Federation: 130
Country: Number of subjects enrolled	South Africa: 17
Country: Number of subjects enrolled	Korea, Republic of: 124
Country: Number of subjects enrolled	Spain: 35

Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	Turkey: 42
Country: Number of subjects enrolled	Ukraine: 114
Country: Number of subjects enrolled	United Kingdom: 35
Country: Number of subjects enrolled	United States: 254
Country: Number of subjects enrolled	Vietnam: 8
Worldwide total number of subjects	2133
EEA total number of subjects	870

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)	1742
From 65 to 84 years	319
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

2133 patients were entered. 10 were excluded due to a GCP breach. Of remaining 2123 patients, 1926 entered from SIROCCO/CALIMA, and 197 from ZONDA. 2 patients were not treated, and a total of 447 patients (348 SIROCCO/CALIMA and 99 ZONDA) were enrolled into MELTEMI without completing the full follow-up, thus not in the main analyses.

Pre-assignment

Screening details:

953 participants from study SIROCCO/CALIMA receive benralizumab 30 mg at every 4 weeks schedule. 971 participants from study SIROCCO/CALIMA receive treatment at every 8 weeks schedule. 100 participants from study ZONDA receive treatment at every 4 weeks schedule. 97 participants from study ZONDA receive treatment at every 8 weeks schedule.

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, Carer, Data analyst, Assessor, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks

Arm description:

Benralizumab administered subcutaneously every 4 weeks

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

Dosage and administration details:

30 mg

Arm title	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks

Arm description:

Benralizumab administered subcutaneously every 8 weeks

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

Dosage and administration details:

30 mg

Arm title	ZONDA - Benralizumab 30 mg q.4 weeks

Arm description:

Benralizumab administered subcutaneously every 4 weeks

Arm type	Experimental

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

Dosage and administration details:

30 mg

Arm title	ZONDA - Benralizumab 30 mg q.8 weeks

Arm description:

Benralizumab administered subcutaneously every 8 weeks

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

Dosage and administration details:

30 mg

Number of subjects in period 1[1]	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks	ZONDA - Benralizumab 30 mg q.4 weeks
Started	953	973	100
Treated	953	971	100
Completed	892	871	92
Not completed	61	102	8
Adverse event, serious fatal	5	4	-
Consent withdrawn by subject	20	17	7
Eligibility criteria not fulfilled	-	2	-
Adverse event, non-fatal	3	4	-
Ongoing	19	58	-
study specific discount. criteria	1	1	-
Lost to follow-up	5	10	1
eg. not made to the visit	7	4	-
Protocol deviation	1	2	-

Number of subjects in period 1[1]	ZONDA - Benralizumab 30 mg q.8 weeks
Started	97
Treated	97
Completed	92
Not completed	5
Adverse event, serious fatal	1
Consent withdrawn by subject	1

Eligibility criteria not fulfilled	-
Adverse event, non-fatal	-
Ongoing	-
study specific discount. criteria	-
Lost to follow-up	2
eg. not made to the visit	1
Protocol deviation	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: There are total 2133 enrolled, 10 patients were excluded from all analyses due to GCP breach. Thus there is a 10 patient difference.

Baseline characteristics

Reporting groups	
Reporting group title	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks
Reporting group description: Benralizumab administered subcutaneously every 4 weeks	
Reporting group title	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks
Reporting group description: Benralizumab administered subcutaneously every 8 weeks	
Reporting group title	ZONDA - Benralizumab 30 mg q.4 weeks
Reporting group description: Benralizumab administered subcutaneously every 4 weeks	
Reporting group title	ZONDA - Benralizumab 30 mg q.8 weeks
Reporting group description: Benralizumab administered subcutaneously every 8 weeks	

Reporting group values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks	ZONDA - Benralizumab 30 mg q.4 weeks
Number of subjects	953	973	100
Age categorical			
Two separate summaries presented: Overall all randomized patients (excluding non-GCP compliant patients); Separately for Full analysis set, excluding patients enrolled in MELTEMI.			
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)	21	51	0
Adults (18-64 years)	773	790	86
From 65-84 years	159	132	14
85 years and over	0	0	0
Age Continuous			
Full analysis set, Excluding patients enrolled in MELTEMI			
Units: years			
arithmetic mean	51.1	48.9	49.7
standard deviation	± 13.79	± 15.53	± 10.35
Sex: Female, Male			
Two separate summaries presented: Overall all randomized patients (excluding non-GCP compliant patients); Separately for Full analysis set, excluding patients enrolled in MELTEMI.			
Units: Subjects			
Female	612	584	58
Male	341	389	42
Race/Ethnicity, Customized			
Two separate summaries presented: Overall all randomized patients (excluding non-GCP compliant patients); Separately for Full analysis set, excluding patients enrolled in MELTEMI.			
Units: Subjects			
White	753	774	96

Black and African American	25	30	0
Asian	143	139	4
Other	32	30	0

Reporting group values	ZONDA - Benralizumab 30 mg q.8 weeks	Total	
Number of subjects	97	2123	
Age categorical			
Two separate summaries presented: Overall all randomized patients (excluding non-GCP compliant patients); Separately for Full analysis set, excluding patients enrolled in MELTEMI.			
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	72	
Adults (18-64 years)	83	1732	
From 65-84 years	14	319	
85 years and over	0	0	
Age Continuous			
Full analysis set, Excluding patients enrolled in MELTEMI			
Units: years			
arithmetic mean	52.7		
standard deviation	± 8.90	-	
Sex: Female, Male			
Two separate summaries presented: Overall all randomized patients (excluding non-GCP compliant patients); Separately for Full analysis set, excluding patients enrolled in MELTEMI.			
Units: Subjects			
Female	61	1315	
Male	36	808	
Race/Ethnicity, Customized			
Two separate summaries presented: Overall all randomized patients (excluding non-GCP compliant patients); Separately for Full analysis set, excluding patients enrolled in MELTEMI.			
Units: Subjects			
White	88	1711	
Black and African American	2	57	
Asian	7	293	
Other	0	62	

Subject analysis sets

Subject analysis set title	SIROCCO/CALIMA - Benralizumab 30 mg q.4 - Pre Benra q.4
Subject analysis set type	Full analysis
Subject analysis set description:	
Benralizumab administered subcutaneously every 4 weeks, predecessor study with benralizumab treatment	
Subject analysis set title	SIROCCO/CALIMA - Benralizumab 30 mg q.4 - Predecessor Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Benralizumab administered subcutaneously every 4 weeks, predecessor study with placebo treatment

Subject analysis set title	SIROCCO/CALIMA - Benralizumab 30 mg q.8 - Pre Benra q.8
Subject analysis set type	Full analysis

Subject analysis set description:

Benralizumab administered subcutaneously every 8 weeks, predecessor study with benralizumab treatment

Subject analysis set title	SIROCCO/CALIMA - Benralizumab 30 mg q.8 - Predecessor Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Benralizumab administered subcutaneously every 8 weeks, predecessor study with placebo treatment

Subject analysis set title	ZONDA - Benralizumab 30 mg q.4 - Pre Benra q.4
Subject analysis set type	Full analysis

Subject analysis set description:

Benralizumab administered subcutaneously every 4 weeks, predecessor study with benralizumab treatment

Subject analysis set title	ZONDA - Benralizumab 30 mg q.4 - Predecessor Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Benralizumab administered subcutaneously every 4 weeks, predecessor study with placebo treatment

Subject analysis set title	ZONDA - Benralizumab 30 mg q.8 - Pre Benra q.8
Subject analysis set type	Full analysis

Subject analysis set description:

Benralizumab administered subcutaneously every 8 weeks, predecessor study with benralizumab treatment

Subject analysis set title	ZONDA - Benralizumab 30 mg q.8 - Predecessor Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Benralizumab administered subcutaneously every 8 weeks, predecessor study with placebo treatment

Reporting group values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 - Pre Benra q.4	SIROCCO/CALIMA - Benralizumab 30 mg q.4 - Predecessor Placebo	SIROCCO/CALIMA - Benralizumab 30 mg q.8 - Pre Benra q.8
Number of subjects	518	265	512
Age categorical			
Two separate summaries presented: Overall all randomized patients (excluding non-GCP compliant patients); Separately for Full analysis set, excluding patients enrolled in MELTEMI.			
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)	12	9	25
Adults (18-64 years)	421	213	421
From 65-84 years	85	43	66
85 years and over	0	0	0
Age Continuous			
Full analysis set, Excluding patients enrolled in MELTEMI			
Units: years			
arithmetic mean	51.7	49.9	49.3

standard deviation	± 13.26	± 14.73	± 14.81

Sex: Female, Male			
Two separate summaries presented: Overall all randomized patients (excluding non-GCP compliant patients); Separately for Full analysis set, excluding patients enrolled in MELTEMI.			
Units: Subjects			
Female	339	164	307
Male	179	101	205
Race/Ethnicity, Customized			
Two separate summaries presented: Overall all randomized patients (excluding non-GCP compliant patients); Separately for Full analysis set, excluding patients enrolled in MELTEMI.			
Units: Subjects			
White	398	201	388
Black and African American	6	10	12
Asian	94	44	92
Other	20	10	20

Reporting group values	SIROCCO/CALIMA - Benralizumab 30 mg q.8 - Predecessor Placebo	ZONDA - Benralizumab 30 mg q.4 - Pre Benra q.4	ZONDA - Benralizumab 30 mg q.4 - Predecessor Placebo
Number of subjects	281	31	18
Age categorical			
Two separate summaries presented: Overall all randomized patients (excluding non-GCP compliant patients); Separately for Full analysis set, excluding patients enrolled in MELTEMI.			
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)	26	0	0
Adults (18-64 years)	211	30	16
From 65-84 years	44	1	2
85 years and over	0	0	0
Age Continuous			
Full analysis set, Excluding patients enrolled in MELTEMI			
Units: years			
arithmetic mean	48.2	47.9	52.7
standard deviation	± 16.77	± 10.42	± 9.77
Sex: Female, Male			
Two separate summaries presented: Overall all randomized patients (excluding non-GCP compliant patients); Separately for Full analysis set, excluding patients enrolled in MELTEMI.			
Units: Subjects			
Female	163	13	14
Male	118	18	4
Race/Ethnicity, Customized			
Two separate summaries presented: Overall all randomized patients (excluding non-GCP compliant patients); Separately for Full analysis set, excluding patients enrolled in MELTEMI.			
Units: Subjects			
White	224	28	17
Black and African American	7	0	0

Asian	44	3	1
Other	6	0	0

Reporting group values	ZONDA - Benralizumab 30 mg q.8 - Pre Benra q.8	ZONDA - Benralizumab 30 mg q.8 - Predecessor Placebo	
Number of subjects	31	18	
Age categorical			
Two separate summaries presented: Overall all randomized patients (excluding non-GCP compliant patients); Separately for Full analysis set, excluding patients enrolled in MELTEMI.			
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)	26	17	
From 65-84 years	5	1	
85 years and over	0	0	
Age Continuous			
Full analysis set, Excluding patients enrolled in MELTEMI			
Units: years			
arithmetic mean	54.3	49.9	
standard deviation	± 8.39	± 9.30	
Sex: Female, Male			
Two separate summaries presented: Overall all randomized patients (excluding non-GCP compliant patients); Separately for Full analysis set, excluding patients enrolled in MELTEMI.			
Units: Subjects			
Female	20	9	
Male	11	9	
Race/Ethnicity, Customized			
Two separate summaries presented: Overall all randomized patients (excluding non-GCP compliant patients); Separately for Full analysis set, excluding patients enrolled in MELTEMI.			
Units: Subjects			
White	26	16	
Black and African American	0	1	
Asian	5	1	
Other	0	0	

End points

End points reporting groups

Reporting group title	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks
Reporting group description: Benralizumab administered subcutaneously every 4 weeks	
Reporting group title	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks
Reporting group description: Benralizumab administered subcutaneously every 8 weeks	
Reporting group title	ZONDA - Benralizumab 30 mg q.4 weeks
Reporting group description: Benralizumab administered subcutaneously every 4 weeks	
Reporting group title	ZONDA - Benralizumab 30 mg q.8 weeks
Reporting group description: Benralizumab administered subcutaneously every 8 weeks	
Subject analysis set title	SIROCCO/CALIMA - Benralizumab 30 mg q.4 - Pre Benra q.4
Subject analysis set type	Full analysis
Subject analysis set description: Benralizumab administered subcutaneously every 4 weeks, predecessor study with benralizumab treatment	
Subject analysis set title	SIROCCO/CALIMA - Benralizumab 30 mg q.4 - Predecessor Placebo
Subject analysis set type	Full analysis
Subject analysis set description: Benralizumab administered subcutaneously every 4 weeks, predecessor study with placebo treatment	
Subject analysis set title	SIROCCO/CALIMA - Benralizumab 30 mg q.8 - Pre Benra q.8
Subject analysis set type	Full analysis
Subject analysis set description: Benralizumab administered subcutaneously every 8 weeks, predecessor study with benralizumab treatment	
Subject analysis set title	SIROCCO/CALIMA - Benralizumab 30 mg q.8 - Predecessor Placebo
Subject analysis set type	Full analysis
Subject analysis set description: Benralizumab administered subcutaneously every 8 weeks, predecessor study with placebo treatment	
Subject analysis set title	ZONDA - Benralizumab 30 mg q.4 - Pre Benra q.4
Subject analysis set type	Full analysis
Subject analysis set description: Benralizumab administered subcutaneously every 4 weeks, predecessor study with benralizumab treatment	
Subject analysis set title	ZONDA - Benralizumab 30 mg q.4 - Predecessor Placebo
Subject analysis set type	Full analysis
Subject analysis set description: Benralizumab administered subcutaneously every 4 weeks, predecessor study with placebo treatment	
Subject analysis set title	ZONDA - Benralizumab 30 mg q.8 - Pre Benra q.8
Subject analysis set type	Full analysis
Subject analysis set description: Benralizumab administered subcutaneously every 8 weeks, predecessor study with benralizumab treatment	
Subject analysis set title	ZONDA - Benralizumab 30 mg q.8 - Predecessor Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Benralizumab administered subcutaneously every 8 weeks, predecessor study with placebo treatment

Primary: Change from baseline in lab variables, Full analysis set, Excluding MELTEMI patients

End point title	Change from baseline in lab variables, Full analysis set, Excluding MELTEMI patients[1]

End point description:

Change from baseline in hematologic (Basophils, Leukocytes, Lymphocytes, Neutrophils, Eosinophils) and chemistry tests (ALT, AST, Bilirubin).

End point type	Primary

End point timeframe:

Week 56

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 study is safety follow-up study. All analyses are descriptive and no hypothesis testing was intended or planned.

End point values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks	ZONDA - Benralizumab 30 mg q.4 weeks	ZONDA - Benralizumab 30 mg q.8 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	783	793	49	49
Units: SI unit				
arithmetic mean (standard deviation)				
Basophils (10**9/L)|	-0.005 (± 0.0223)	-0.005 (± 0.0239)	-0.007 (± 0.0283)	-0.005 (± 0.0244)
Leukocytes (10**9/L)|	-0.344 (± 2.0412)	-0.128 (± 1.8614)	-0.808 (± 1.8177)	-0.507 (± 3.3612)
Lymphocytes (10**9/L)|	-0.032 (± 0.6242)	0.003 (± 0.5402)	-0.093 (± 0.6403)	0.007 (± 0.6864)
Neutrophils (10**9/L)|	-0.171 (± 1.8746)	0.013 (± 1.7024)	-0.501 (± 1.7096)	-0.368 (± 3.2057)
Eosinophils (10**9/L)|	-0.1220 (± 0.30599)	-0.1271 (± 0.26161)	-0.1451 (± 0.30766)	-0.1664 (± 0.35139)
Alanine Aminotransferase (ukat/L)|	-0.007 (± 0.2102)	0.017 (± 0.4651)	-0.064 (± 0.3547)	-0.023 (± 0.1940)
Aspartate Aminotransferase (ukat/L)|	-0.005 (± 0.1431)	0.004 (± 0.3303)	-0.027 (± 0.2291)	-0.026 (± 0.1178)
Bilirubin (umol/L)|	0.187 (± 3.6261)	0.391 (± 3.9945)	0.146 (± 2.8094)	0.279 (± 3.8765)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of overall patients with asthma exacerbations during study period, Full analysis set, Excluding MELTEMI patients

End point title	Number of overall patients with asthma exacerbations during study period, Full analysis set, Excluding MELTEMI patients

End point description:

Annual asthma exacerbation rate, where an asthma exacerbation is defined by a worsening of asthma

requiring the use of systemic corticosteroids for at least 3 days, and/or an in patient hospitalization, and/or an emergency department or urgent care visit

End point type	Secondary

End point timeframe:

From week 0 to week 56 in study treatment period and through the follow up period (16 weeks from day of last dose)

End point values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks	ZONDA - Benralizumab 30 mg q.4 weeks	ZONDA - Benralizumab 30 mg q.8 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	783	793	49	49
Units: participants				
Sirocco/Calima eos>=300/µL|# exacerb.	159	170	0	0
Sirocco/Calima eos<300/µL|# exacerb.	113	97	0	0
Zonda|# of exacerbation	0	0	17	24

End point values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 - Pre Benra q.4	SIROCCO/CALIMA - Benralizumab 30 mg q.4 - Predecessor Placebo	SIROCCO/CALIMA - Benralizumab 30 mg q.8 - Pre Benra q.8	SIROCCO/CALIMA - Benralizumab 30 mg q.8 - Predecessor Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	518	265	512	281
Units: participants				
Sirocco/Calima eos>=300/µL|# exacerb.	99	60	104	66
Sirocco/Calima eos<300/µL|# exacerb.	69	44	65	32
Zonda|# of exacerbation	0	0	0	0

End point values	ZONDA - Benralizumab 30 mg q.4 - Pre Benra q.4	ZONDA - Benralizumab 30 mg q.4 - Predecessor Placebo	ZONDA - Benralizumab 30 mg q.8 - Pre Benra q.8	ZONDA - Benralizumab 30 mg q.8 - Predecessor Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	18	31	18
Units: participants				
Sirocco/Calima eos>=300/µL|# exacerb.	0	0	0	0
Sirocco/Calima eos<300/µL|# exacerb.	0	0	0	0
Zonda|# of exacerbation	12	5	13	11

Statistical analyses

No statistical analyses for this end point

Secondary: Annual asthma exacerbation rate during on-treatment period, Full analysis set, Excluding MELTEMI patients

End point title	Annual asthma exacerbation rate during on-treatment period, Full analysis set, Excluding MELTEMI patients

End point description:

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

End point type	Secondary

End point timeframe:

From week 0 to week 56 in study treatment period.

End point values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks	ZONDA - Benralizumab 30 mg q.4 weeks	ZONDA - Benralizumab 30 mg q.8 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	783[2]	793[3]	49[4]	49[5]
Units: count per year				
number (confidence interval 95%)				
Sirocco/Calima patients with EOS>=300/µL	0.5 (0.44 to 0.56)	0.49 (0.44 to 0.56)	0 (0 to 0)	0 (0 to 0)
Sirocco/Calima patients with EOS<300/µL	0.76 (0.66 to 0.87)	0.64 (0.55 to 0.74)	0 (0 to 0)	0 (0 to 0)
Zonda patients	0 (0 to 0)	0 (0 to 0)	0.63 (0.44 to 0.91)	0.68 (0.48 to 0.95)

Notes:

[2] - 519 for EOS>=300
264 for EOS<300

[3] - 527 for EOS>=300
266 for EOS<300

[4] - Over all EOS

[5] - Over all EOS

End point values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 - Pre Benra q.4	SIROCCO/CALIMA - Benralizumab 30 mg q.4 - Predecessor Placebo	SIROCCO/CALIMA - Benralizumab 30 mg q.8 - Pre Benra q.8	SIROCCO/CALIMA - Benralizumab 30 mg q.8 - Predecessor Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	518[6]	265[7]	512[8]	281[9]
Units: count per year				

number (confidence interval 95%)				
Sirocco/Calima patients with EOS>=300/µL	0.48 (0.42 to 0.56)	0.53 (0.43 to 0.56)	0.59 (0.49 to 0.71)	0.74 (0.59 to 0.94)
Sirocco/Calima patients with EOS<300/µL	0.74 (0.62 to 0.88)	0.8 (0.64 to 1)	0.59 (0.49 to 0.71)	0.74 (0.59 to 0.94)
Zonda patients	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)

Notes:

[6] - 347 for EOS>=300
171 for EOS<300
[7] - 172 for EOS>=300
93 for EOS<300
[8] - 339 for EOS>=300
173 for EOS<300
[9] - 188 for EOS>=300
93 for EOS<300

End point values	ZONDA - Benralizumab 30 mg q.4 - Pre Benra q.4	ZONDA - Benralizumab 30 mg q.4 - Predecessor Placebo	ZONDA - Benralizumab 30 mg q.8 - Pre Benra q.8	ZONDA - Benralizumab 30 mg q.8 - Predecessor Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31[10]	18[11]	31[12]	18[13]
Units: count per year				
number (confidence interval 95%)				
Sirocco/Calima patients with EOS>=300/µL	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Sirocco/Calima patients with EOS<300/µL	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Zonda patients	0.6 (0.39 to 0.95)	0.7 (0.38 to 1.3)	0.64 (0.42 to 0.98)	0.75 (0.44 to 1.3)

Notes:

[10] - Over all EOS

[11] - Over all EOS

[12] - Over all EOS

[13] - Over all EOS

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in pre-brochodilator FEV1 (L), Full analysis set, Excluding MELTEMI patients

End point title	Change from baseline in pre-brochodilator FEV1 (L), Full analysis set, Excluding MELTEMI patients

End point description:

Change from baseline to Week 56 in Pre-bronchodilator Forced expiratory volume in 1 second (FEV1).

End point type	Secondary

End point timeframe:

Week 56

End point values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks	ZONDA - Benralizumab 30 mg q.4 weeks	ZONDA - Benralizumab 30 mg q.8 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	665[14]	660[15]	38[16]	43[17]
Units: Liter				
arithmetic mean (standard deviation)				
Sirocco/Calima patients with EOS>=300/µL	0.038 (± 0.346)	0.040 (± 0.356)	0 (± 0)	0 (± 0)
Sirocco/Calima patients with EOS<300/µL	-0.017 (± 0.345)	-0.001 (± 0.312)	0 (± 0)	0 (± 0)
Zonda patients	0 (± 0)	0 (± 0)	0.057 (± 0.412)	-0.012 (± 0.314)

Notes:

[14] - 439 for EOS>=300
226 for EOS<300

[15] - 442 for EOS>=300
218 for EOS<300

[16] - Over all EOS

[17] - Over all EOS

End point values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 - Pre Benra q.4	SIROCCO/CALIMA - Benralizumab 30 mg q.4 - Predecessor Placebo	SIROCCO/CALIMA - Benralizumab 30 mg q.8 - Pre Benra q.8	SIROCCO/CALIMA - Benralizumab 30 mg q.8 - Predecessor Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	444[18]	221[19]	440[20]	220[21]
Units: Liter				
arithmetic mean (standard deviation)				
Sirocco/Calima patients with EOS>=300/µL	-0.006 (± 0.295)	0.131 (± 0.422)	0.019 (± 0.317)	0.081 (± 0.419)
Sirocco/Calima patients with EOS<300/µL	-0.021 (± 0.376)	-0.011 (± 0.280)	-0.015 (± 0.293)	0.030 (± 0.350)
Zonda patients	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)

Notes:

[18] - 297 for EOS>=300
147 for EOS<300

[19] - 142 for EOS>=300
79 for EOS<300

[20] - 291 for EOS>=300
149 for EOS<300

[21] - 151 for EOS>=300
69 for EOS<300

End point values	ZONDA - Benralizumab 30 mg q.4 - Pre Benra q.4	ZONDA - Benralizumab 30 mg q.4 - Predecessor Placebo	ZONDA - Benralizumab 30 mg q.8 - Pre Benra q.8	ZONDA - Benralizumab 30 mg q.8 - Predecessor Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	27[22]	11[23]	28[24]	15[25]
Units: Liter				
arithmetic mean (standard deviation)				
Sirocco/Calima patients with EOS>=300/µL	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Sirocco/Calima patients with EOS<300/µL	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)

Zonda patients	0.013 (± 0.354)	0.167 (± 0.533)	-0.093 (± 0.280)	0.138 (± 0.329)

Notes:

[22] - Over all EOS

[23] - Over all EOS

[24] - Over all EOS

[25] - Over all EOS

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in post-brochodilator FEV1 (L), Full analysis set, Excluding MELTEMI patients

End point title	Change from baseline in post-brochodilator FEV1 (L), Full analysis set, Excluding MELTEMI patients[26]

End point description:

Change from baseline to Week 56 in Post-bronchodilator Forced expiratory volume in 1 second (FEV1).

End point type	Secondary

End point timeframe:

Week 56

Notes:

[26] - 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: Patients in two arms from study ZONDA were not required to collect post-bronchodilator FEV1, thus this endpoint was not analyzed for those two arms.

End point values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks	SIROCCO/CALIMA - Benralizumab 30 mg q.4 - Pre Benra q.4	SIROCCO/CALIMA - Benralizumab 30 mg q.4 - Predecessor Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	659[27]	652[28]	439[29]	220[30]
Units: Liter				
arithmetic mean (standard deviation)				
Sirocco/Calima patients with eos>=300/µL	-0.015 (± 0.354)	-0.004 (± 0.329)	-0.066 (± 0.280)	0.089 (± 0.455)
Sirocco/Calima patients with eos<300/µL	-0.046 (± 0.350)	-0.015 (± 0.316)	-0.058 (± 0.379)	-0.024 (± 0.289)

Notes:

[27] - 440 for EOS>=300
219 for EOS<300

[28] - 443 for EOS>=300
209 for EOS<300

[29] - 296 for EOS>=300
143 for EOS<300

[30] - 144 for EOS>=300
76 for EOS<300

End point values	SIROCCO/CALIMA - Benralizumab 30 mg q.8 - Pre Benra q.8	SIROCCO/CALIMA - Benralizumab 30 mg q.8 - Predecessor Placebo		

Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	438[31]	214[32]		
Units: Liter				
arithmetic mean (standard deviation)				
Sirocco/Calima patients with eos>=300/µL	-0.029 (± 0.281)	0.045 (± 0.401)		
Sirocco/Calima patients with eos<300/µL	-0.043 (± 0.273)	0.049 (± 0.394)		

Notes:

[31] - 292 for EOS>=300
146 for EOS<300
[32] - 151 for EOS>=300
63 for EOS<300

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Asthma Control Questionnaire (ACQ) as a measure of asthma control in overall patients, Full analysis set, Excluding MELTEMI patients

End point title	Change from baseline in Asthma Control Questionnaire (ACQ) as a measure of asthma control in overall patients, Full analysis set, Excluding MELTEMI patients

End point description:

Asthma Control Questionnaire 6 (ACQ-6) contains 1 bronchodilator use question and 5 symptom questions. Questions were weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score was the mean of the responses.

End point type	Secondary

End point timeframe:

Week 56

End point values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks	ZONDA - Benralizumab 30 mg q.4 weeks	ZONDA - Benralizumab 30 mg q.8 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	671[33]	664[34]	39[35]	43[36]
Units: Scale of score				
arithmetic mean (standard deviation)				
Sirocco/Calima patients with eos>=300/µL	-0.09 (± 0.91)	-0.12 (± 0.91)	0 (± 0)	0 (± 0)
Sirocco/Calima patients with eos<300/µL	-0.15 (± 0.86)	-0.10 (± 0.90)	0 (± 0)	0 (± 0)
Zonda patients	0 (± 0)	0 (± 0)	-0.21 (± 0.87)	-0.05 (± 1.04)

Notes:

[33] - 444 for EOS>=300
227 for EOS<300
[34] - 447 for EOS>=300
217 for EOS<300
[35] - Over all EOS
[36] - Over all EOS

End point values	SIROCCO/CALI	SIROCCO/CALI	SIROCCO/CALI	SIROCCO/CALI

	MA - Benralizumab 30 mg q.4 - Pre Benra q.4	MA - Benralizumab 30 mg q.4 - Predecessor Placebo	MA - Benralizumab 30 mg q.8 - Pre Benra q.8	MA - Benralizumab 30 mg q.8 - Predecessor Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	447[37]	224[38]	444[39]	220[40]
Units: Scale of score				
arithmetic mean (standard deviation)				
Sirocco/Calima patients with eos>=300/µL	-0.04 (± 0.83)	-0.20 (± 1.04)	-0.06 (± 0.82)	-0.25 (± 1.06)
Sirocco/Calima patients with eos<300/µL	-0.16 (± 0.90)	-0.12 (± 0.80)	-0.10 (± 0.83)	-0.09 (± 1.06)
Zonda patients	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)

Notes:

[37] - 298 for EOS>=300
149 for EOS<300
[38] - 146 for EOS>=300
78 for EOS<300
[39] - 294 for EOS>=300
150 for EOS<300
[40] - 153 for EOS>=300
67 for EOS<300

End point values	ZONDA - Benralizumab 30 mg q.4 - Pre Benra q.4	ZONDA - Benralizumab 30 mg q.4 - Predecessor Placebo	ZONDA - Benralizumab 30 mg q.8 - Pre Benra q.8	ZONDA - Benralizumab 30 mg q.8 - Predecessor Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	28[41]	11[42]	28[43]	15[44]
Units: Scale of score				
arithmetic mean (standard deviation)				
Sirocco/Calima patients with eos>=300/µL	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Sirocco/Calima patients with eos<300/µL	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Zonda patients	-0.05 (± 0.89)	-0.61 (± 0.74)	0.15 (± 1.02)	-0.43 (± 1.00)

Notes:

[41] - Over all EOS

[42] - Over all EOS

[43] - Over all EOS

[44] - Over all EOS

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in total score of asthma related and general health-related quality of life questionnaire (AQLQ(S)+12), Full analysis set, Excluding MELTEMI patients

End point title	Change from baseline in total score of asthma related and general health-related quality of life questionnaire (AQLQ(S)+12), Full analysis set, Excluding MELTEMI patients

End point description:

Standardised Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ(S)+12) comprises 4 separate domains (symptoms, activity limitations, emotional function, and environmental stimuli). An increase in score indicates improvement.

End point type	Secondary

End point timeframe:
Week 56

End point values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks	ZONDA - Benralizumab 30 mg q.4 weeks	ZONDA - Benralizumab 30 mg q.8 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	668[45]	662[46]	37[47]	43[48]
Units: Scale of score				
arithmetic mean (standard deviation)				
Sirocco/Calima patients with eos>=300/µL	0.08 (± 0.87)	0.15 (± 0.94)	0 (± 0)	0 (± 0)
Sirocco/Calima patients with eos<300/µL	0.09 (± 0.85)	0.11 (± 0.95)	0 (± 0)	0 (± 0)
Zonda patients|	0 (± 0)	0 (± 0)	0.22 (± 0.92)	0.11 (± 0.98)

Notes:

[45] - 442 for EOS>=300
226 for EOS<300
[46] - 446 for EOS>=300
216 for EOS<300
[47] - Over all EOS

[48] - Over all EOS

End point values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 - Pre Benra q.4	SIROCCO/CALIMA - Benralizumab 30 mg q.4 - Predecessor Placebo	SIROCCO/CALIMA - Benralizumab 30 mg q.8 - Pre Benra q.8	SIROCCO/CALIMA - Benralizumab 30 mg q.8 - Predecessor Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	444[49]	224[50]	442[51]	220[52]
Units: Scale of score				
arithmetic mean (standard deviation)				
Sirocco/Calima patients with eos>=300/µL	0.02 (± 0.80)	0.21 (± 0.98)	0.08 (± 0.91)	0.26 (± 1.00)
Sirocco/Calima patients with eos<300/µL	0.11 (± 0.84)	0.03 (± 0.89)	0.15 (± 0.90)	0.02 (± 1.06)
Zonda patients|	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)

Notes:

[49] - 296 for EOS>=300
148 for EOS<300
[50] - 146 for EOS>=300
78 for EOS<300
[51] - 293 for EOS>=300
149 for EOS<300
[52] - 153 for EOS>=300
67 for EOS<300

End point values	ZONDA - Benralizumab 30 mg q.4 - Pre Benra q.4	ZONDA - Benralizumab 30 mg q.4 - Predecessor Placebo	ZONDA - Benralizumab 30 mg q.8 - Pre Benra q.8	ZONDA - Benralizumab 30 mg q.8 - Predecessor Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	26[53]	11[54]	28[55]	15[56]

Units: Scale of score				
arithmetic mean (standard deviation)				
Sirocco/Calima patients with eos>=300/µL	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Sirocco/Calima patients with eos<300/µL	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Zonda patients|	0.13 (± 0.93)	0.43 (± 0.91)	-0.04 (± 0.94)	0.40 (± 1.03)

Notes:

[53] - Over all EOS

[54] - Over all EOS

[55] - Over all EOS

[56] - Over all EOS

Statistical analyses

No statistical analyses for this end point

Secondary: Change of blood eosinophil levels' measurement in overall patients, Full analysis set, Excluding MELTEMI patients

End point title	Change of blood eosinophil levels' measurement in overall patients, Full analysis set, Excluding MELTEMI patients

End point description:

Change from baseline to Week 56 in Blood eosinophils

End point type	Secondary

End point timeframe:

Week 56

End point values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks	ZONDA - Benralizumab 30 mg q.4 weeks	ZONDA - Benralizumab 30 mg q.8 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	691[57]	703[58]	39[59]	42[60]
Units: cell/µL				
arithmetic mean (standard deviation)				
Sirocco/Calima patients with eos>=300/µL	-148.6 (± 332.91)	-154.1 (± 297.34)	0 (± 0)	0 (± 0)
Sirocco/Calima patients with eos<300/µL	-68.4 (± 234.40)	-74.7 (± 160.29)	0 (± 0)	0 (± 0)
Zonda patients	0 (± 0)	0 (± 0)	-145.1 (± 307.66)	-166.4 (± 351.39)

Notes:

[57] - 462 for EOS>=300
229 for EOS<300

[58] - 464 for EOS>=300
239 for EOS<300

[59] - Over all EOS

[60] - Over all EOS

End point values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 -	SIROCCO/CALIMA - Benralizumab 30 mg q.4 -	SIROCCO/CALIMA - Benralizumab 30 mg q.8 -	SIROCCO/CALIMA - Benralizumab 30 mg q.8 -

	Pre Benra q.4	Predecessor Placebo	Pre Benra q.8	Predecessor Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	454[61]	237[62]	461[63]	242[64]
Units: cell/µL				
arithmetic mean (standard deviation)				
Sirocco/Calima patients with eos>=300/µL	4.9 (± 177.42)	-449.6 (± 360.6)	-10.1 (± 134.7)	-422.5 (± 330.01)
Sirocco/Calima patients with eos<300/µL	15.7 (± 87.04)	-222.1 (± 325.03)	-2.9 (± 59.11)	-217.4 (± 198.56)
Zonda patients	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)

Notes:

[61] - 306 for EOS>=300
148 for EOS<300

[62] - 156 for EOS>=300
81 for EOS<300

[63] - 302 for EOS>=300
159 for EOS<300

[64] - 162 for EOS>=300
80 for EOS<300

End point values	ZONDA - Benralizumab 30 mg q.4 - Pre Benra q.4	ZONDA - Benralizumab 30 mg q.4 - Predecessor Placebo	ZONDA - Benralizumab 30 mg q.8 - Pre Benra q.8	ZONDA - Benralizumab 30 mg q.8 - Predecessor Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	28[65]	11[66]	27[67]	15[68]
Units: cell/µL				
arithmetic mean (standard deviation)				
Sirocco/Calima patients with eos>=300/µL	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Sirocco/Calima patients with eos<300/µL	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Zonda patients	2.5 (± 69.85)	-520.9 (± 360.79)	-17.0 (± 107.48)	-435.3 (± 468.64)

Notes:

[65] - Over all EOS

[66] - Over all EOS

[67] - Over all EOS

[68] - Over all EOS

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in EQ-5D-5L visual analog scale, Full analysis set, Excluding MELTEMI patients

End point title	Change from baseline in EQ-5D-5L visual analog scale, Full analysis set, Excluding MELTEMI patients

End point description:

The questionnaire included a VAS, where the patient was asked to rate current health status on a scale of 0 to 100, with 0 being the worst imaginable health state; thus, an increase in VAS score indicated improvement.

End point type	Secondary

End point timeframe:

Week 56

End point values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks	ZONDA - Benralizumab 30 mg q.4 weeks	ZONDA - Benralizumab 30 mg q.8 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	682[69]	709[70]	21[71]	28[72]
Units: Scale of score				
arithmetic mean (standard deviation)				
Sirocco/Calima patients with eos>=300/µL	6.08 (± 15.68)	6.02 (± 17.68)	0 (± 0)	0 (± 0)
Sirocco/Calima patients with eos<300/µL	4.38 (± 14.99)	6.69 (± 15.96)	0 (± 0)	0 (± 0)
Zonda patients	0 (± 0)	0 (± 0)	5.00 (± 10.35)	1.36 (± 13.58)

Notes:

[69] - 454 for EOS>=300
228 for EOS<3000
[70] - 468 for EOS>=300
241 for EOS<300
[71] - Over all EOS

[72] - Over all EOS

Statistical analyses

No statistical analyses for this end point

Secondary: Work Productivity loss in adults, using Work Productivity and Activity Impairment Questionnaire (WPAI), Full analysis set, Excluding MELTEMI patients

End point title	Work Productivity loss in adults, using Work Productivity and Activity Impairment Questionnaire (WPAI), Full analysis set, Excluding MELTEMI patients

End point description:

The WPAI+CIQ is a 10-item questionnaire that assesses productivity and activity impairment over the previous week. The questionnaire includes hours missed from work/school due to asthma, degree health affected productivity while at work/school, as well as the degree to which health affected regular activities other than work or school. The questionnaire related to the previous 7 days.

End point type	Secondary

End point timeframe:

Baseline and Week 68

End point values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks	ZONDA - Benralizumab 30 mg q.4 weeks	ZONDA - Benralizumab 30 mg q.8 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	783[73]	793[74]	49[75]	49[76]
Units: percentage				
arithmetic mean (standard deviation)				
Sirocco/Calima patients with eos>=300/µL-baseline	25.3 (± 24.70)	25.0 (± 24.15)	0 (± 0)	0 (± 0)

Sirocco/Calima patients with eos>=300/µL-wk 68	23.3 (± 26.18)	21.0 (± 25.54)	0 (± 0)	0 (± 0)
Sirocco/Calima patients with eos<300/µL-baseline	31.0 (± 27.06)	32.6 (± 26.29)	0 (± 0)	0 (± 0)
Sirocco/Calima patients with eos<300/µL-wk 68	32.7 (± 27.55)	25.8 (± 24.05)	0 (± 0)	0 (± 0)
Zonda Patients-baseline	0 (± 0)	0 (± 0)	23.5 (± 25.13)	7.1 (± 10.47)
Zonda Patients-wk 68	0 (± 0)	0 (± 0)	18.9 (± 24.94)	21.0 (± 27.13)

Notes:

[73] - BS: 234 for EOS>=300
WK68: 236 for EOS>=300
BS: 101 for EOS<300
WK68: 97 for EOS<300

[74] - BS: 217 for EOS>=300
WK68: 217 for EOS>=300
BS: 93 for EOS<300
WK68: 96 for EOS<300

[75] - BS: 16
WK68: 19

[76] - BS: 17
WK68: 20

Statistical analyses

No statistical analyses for this end point

Secondary: Classroom Productivity loss in adolescents, using Classroom Impairment Questionnaire (CIQ), Full analysis set, Excluding MELTEMI patients

End point title	Classroom Productivity loss in adolescents, using Classroom Impairment Questionnaire (CIQ), Full analysis set, Excluding MELTEMI patients[77]

End point description:

The WPAI (+CIQ) is a 10-item questionnaire that assesses productivity and activity impairment over the previous week. The questionnaire includes hours missed from work/school due to asthma, degree health affected productivity while at work/school, as well as the degree to which health affected regular activities other than work or school. The questionnaire related to the previous 7 days.

End point type	Secondary

End point timeframe:

Baseline and Week 56

Notes:

[77] - 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: Since two arms from study ZONDA, for which does not have adolescent patients, thus this endpoint was not analyzed for those two arms.

End point values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[78]	61[79]		
Units: Percentage				
arithmetic mean (standard deviation)				
Sirocco/Calima patients with eos>=300/µL-Baseline	13.0 (± 19.14)	30.7 (± 31.41)		
Sirocco/Calima patients with eos>=300/µL-wk 56	3.8 (± 7.44)	15.2 (± 20.69)		
Sirocco/Calima patients with eos<300/µL-Baseline	42.1 (± 32.50)	35.4 (± 23.92)		

Sirocco/Calima patients with eos<300/µL-wk 56	5.0 (± 7.07)	17.1 (± 20.06)		

Notes:

[78] - BS: 11 for EOS>=300
WK56: 8 for EOS>=300
BS: 4 for EOS<300
WK56: 2 for EOS<300

[79] - BS: 23 for EOS>=300
WK56: 24 for EOS>=300
BS: 19 for EOS<300
WK56: 24 for EOS<300

Statistical analyses

No statistical analyses for this end point

Secondary: Activity impairment (%), using Work Productivity and Activity Impairment Questionnaire (WPAI), Full analysis set, Excluding MELTEMI patients

End point title	Activity impairment (%), using Work Productivity and Activity Impairment Questionnaire (WPAI), Full analysis set, Excluding MELTEMI patients

End point description:

The WPAI+CIQ is a 10-item questionnaire that assesses productivity and activity impairment over the previous week. The questionnaire includes hours missed from work/school due to asthma, degree health affected productivity while at work/school, as well as the degree to which health affected regular activities other than work or school. The questionnaire related to the previous 7 days. The WPAI+CIQ outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

End point type	Secondary

End point timeframe:

Baseline and Week 68

End point values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks	ZONDA - Benralizumab 30 mg q.4 weeks	ZONDA - Benralizumab 30 mg q.8 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	783[80]	793[81]	49[82]	49[83]
Units: percentage				
arithmetic mean (standard deviation)				
Sirocco/Calima patients with eos>=300/µL-baseline	31.3 (± 26.44)	31.2 (± 25.63)	0 (± 0)	0 (± 0)
Sirocco/Calima patients with eos>=300/µL-wk 68	26.6 (± 26.14)	24.4 (± 25.26)	0 (± 0)	0 (± 0)
Sirocco/Calima patients with eos<300/µL-baseline	39.6 (± 25.75)	36.3 (± 25.72)	0 (± 0)	0 (± 0)
Sirocco/Calima patients with eos<300/µL-wk 68	33.6 (± 26.55)	32.7 (± 26.58)	0 (± 0)	0 (± 0)
Zonda Patients-baseline	0 (± 0)	0 (± 0)	31.5 (± 29.49)	24.5 (± 29.08)
Zonda Patients-wk 68	0 (± 0)	0 (± 0)	28.4 (± 27.85)	39.0 (± 34.36)

Notes:

[80] - BS: 518 for EOS>=300
WK68: 458 for EOS>=300
BS: 261 for EOS<300
WK68: 239 for EOS<300

[81] - BS: 524 for EOS>=300
WK68: 454 for EOS>=300
BS: 264 for EOS<300
WK68: 220 for EOS<300
[82] - BS: 26
WK68: 38
[83] - BS: 31
WK68: 41

Statistical analyses

No statistical analyses for this end point

Secondary: Health care encounters in overall patients on study period, Full analysis set, Excluding MELTEMI patients

End point title	Health care encounters in overall patients on study period, Full analysis set, Excluding MELTEMI patients

End point description:

Hospitalizations, ED visits, urgent care visits and all other outpatient visits due to asthma

End point type	Secondary

End point timeframe:

From week 0 to week 68 in study treatment period and through the follow up period (16 weeks from day of last dose)

End point values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks	ZONDA - Benralizumab 30 mg q.4 weeks	ZONDA - Benralizumab 30 mg q.8 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	519[84]	527[85]	49[86]	49[87]
Units: Participants				
Sirocco/Calima patients with eos>=300/µL	193	198	0	0
Sirocco/Calima patients with eos<300/µL	118	102	0	0
Zonda patients	0	0	20	25

Notes:

[84] - 519 for EOS>=300
264 for EOS<300
[85] - 527 for EOS>=300
266 for EOS<300
[86] - Over all EOS

[87] - Over all EOS

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose benralizumab concentration in serum during the treatment phase of the safety study

End point title	Pre-dose benralizumab concentration in serum during the treatment phase of the safety study

End point description:

Endpoint: Pharmacokinetic (PK) parameters

End point type	Secondary
End point timeframe: Week 0 and Week 56	

End point values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 - Pre Benra q.4	SIROCCO/CALIMA - Benralizumab 30 mg q.4 - Predecessor Placebo	SIROCCO/CALIMA - Benralizumab 30 mg q.8 - Pre Benra q.8	SIROCCO/CALIMA - Benralizumab 30 mg q.8 - Predecessor Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	514[88]	263[89]	511[90]	279[91]
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Baseline	714.25 (± 311.38)	0 (± 0)	142.92 (± 353.94)	0 (± 0)
Week 56	930.04 (± 200.59)	865.93 (± 242.55)	173.95 (± 269.62)	162.03 (± 295.05)

Notes:

[88] - 507 for Baseline
442 for Week 56
[89] - 260 for Baseline
225 for Week 56
[90] - 503 for Baseline
440 for Week 56
[91] - 275 for Baseline
215 for Week 56

End point values	ZONDA - Benralizumab 30 mg q.4 - Pre Benra q.4	ZONDA - Benralizumab 30 mg q.4 - Predecessor Placebo	ZONDA - Benralizumab 30 mg q.8 - Pre Benra q.8	ZONDA - Benralizumab 30 mg q.8 - Predecessor Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31[92]	16[93]	31[94]	17[95]
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Baseline	964.21 (± 224.01)	0 (± 0)	692.91 (± 205.97)	0 (± 0)
Week 56	823.62 (± 239.39)	1160.58 (± 48.82)	247.26 (± 133.0)	139.35 (± 274.98)

Notes:

[92] - 31 for Baseline
27 for Week 56
[93] - 16 for Baseline
10 for Week 56
[94] - 30 for Baseline
27 for Week 56
[95] - 17 for Baseline
15 for Week 56

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-drug antibodies (ADA) responses over all patients, Full analysis set, Excluding MELTEMI patients

End point title	Anti-drug antibodies (ADA) responses over all patients, Full analysis set, Excluding MELTEMI patients

End point description:

Assessments for the presence of ADA and nAb throughout study

End point type	Secondary

End point timeframe:

From week 0 to week 56 in study treatment period (adults) and plus 16 weeks the follow up period; From week 0 to week 108-week in study treatment period (adolescents) and plus 16 weeks the follow up period

End point values	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks	ZONDA - Benralizumab 30 mg q.4 weeks	ZONDA - Benralizumab 30 mg q.8 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	783	793	49	49
Units: Participants				
Positive at any visit|	80	93	4	8
Base- and Post-baseline Positive	23	41	2	4
Newly Persistently Positive	28	34	1	3
Stable persistently positive	21	29	2	2
Newly treatment-induced positive	38	41	2	2
ADA treatment boosted positive	6	6	0	1
Decreased in titre	17	9	2	1
Only post-baseline positive	48	48	2	1
ADA incidence	44	47	2	3
Transiently Positive	22	26	1	3
Only baseline positive	9	4	0	0
nAb positive	57	75	3	4

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adults participants collected events during the entire study period. Adolescents data collection up to last adolescent completed Week 56 visit, which is April 20, 2017.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks

Reporting group description:

Benralizumab administered subcutaneously every 4 weeks

Reporting group title	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks

Reporting group description:

Benralizumab administered subcutaneously every 8 weeks

Reporting group title	ZONDA - Benralizumab 30 mg q.4 weeks

Reporting group description:

Benralizumab administered subcutaneously every 4 weeks

Reporting group title	ZONDA - Benralizumab 30 mg q.8 weeks

Reporting group description:

Benralizumab administered subcutaneously every 8 weeks

Serious adverse events	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks	ZONDA - Benralizumab 30 mg q.4 weeks
Total subjects affected by serious adverse events			
subjects affected / exposed	101 / 783 (12.90%)	93 / 793 (11.73%)	10 / 49 (20.41%)
number of deaths (all causes)	5	4	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
B-cell lymphoma			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			

subjects affected / exposed	2 / 783 (0.26%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign neoplasm of eyelid			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign neoplasm of thyroid gland			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer stage 0			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse large B-cell lymphoma stage II			
subjects affected / exposed	2 / 783 (0.26%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine benign neoplasm			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipoma			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal cavity cancer			

subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondroma			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian germ cell teratoma benign			
subjects affected / exposed	0 / 783 (0.00%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 783 (0.00%)	2 / 793 (0.25%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Solid pseudopapillary tumour of the pancreas			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thymoma			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	1 / 783 (0.13%)	2 / 793 (0.25%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive emergency			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			

subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	2 / 783 (0.26%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food allergy			
subjects affected / exposed	0 / 783 (0.00%)	2 / 793 (0.25%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cervical polyp			

subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal fistula			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	35 / 783 (4.47%)	26 / 793 (3.28%)	3 / 49 (6.12%)
occurrences causally related to treatment / all	0 / 39	1 / 31	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Asthmatic crisis			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Middle lobe syndrome			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal polyps			

subjects affected / exposed	2 / 783 (0.26%)	2 / 793 (0.25%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status asthmaticus			
subjects affected / exposed	1 / 783 (0.13%)	2 / 793 (0.25%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Investigations			
Endocrine test abnormal			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone contusion			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	0 / 783 (0.00%)	0 / 793 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fall			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple fractures			

subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			

subjects affected / exposed	1 / 783 (0.13%)	2 / 793 (0.25%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 783 (0.13%)	2 / 793 (0.25%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congestive cardiomyopathy			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery insufficiency			

subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular extrasystoles			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Diabetic neuropathy			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 783 (0.00%)	2 / 793 (0.25%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lumbosacral radiculopathy			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 783 (0.13%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			

subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Hypochromic anaemia			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 783 (0.00%)	0 / 793 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Barrett's oesophagus			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Colitis ulcerative			
subjects affected / exposed	0 / 783 (0.00%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral hernia strangulated			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	2 / 783 (0.26%)	0 / 793 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Irritable bowel syndrome			

subjects affected / exposed	1 / 783 (0.13%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal ulcer			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 783 (0.13%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			

subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	2 / 783 (0.26%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erythema nodosum			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pemphigoid			
subjects affected / exposed	0 / 783 (0.00%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rosacea			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria papular			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			

subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	2 / 783 (0.26%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperparathyroidism			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 783 (0.13%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Jaw cyst			
subjects affected / exposed	0 / 783 (0.00%)	0 / 793 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 783 (0.00%)	2 / 793 (0.25%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 783 (0.00%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	2 / 783 (0.26%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 783 (0.00%)	0 / 793 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			

subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis salmonella			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	2 / 783 (0.26%)	2 / 793 (0.25%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 783 (0.00%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection viral			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 783 (0.26%)	4 / 793 (0.50%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 783 (0.13%)	5 / 793 (0.63%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative abscess			

subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	1 / 783 (0.13%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sinusitis			
subjects affected / exposed	1 / 783 (0.13%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis bacterial			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 783 (0.00%)	1 / 793 (0.13%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 783 (0.13%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obesity			
subjects affected / exposed	0 / 783 (0.00%)	0 / 793 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	2 / 783 (0.26%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	ZONDA - Benralizumab 30 mg q.8 weeks		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 49 (18.37%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
B-cell lymphoma			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			

subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Benign neoplasm of eyelid				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Benign neoplasm of thyroid gland				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic myeloid leukaemia				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colon cancer stage 0				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diffuse large B-cell lymphoma stage II				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestine benign neoplasm				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lipoma				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nasal cavity cancer				

subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteochondroma				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ovarian germ cell teratoma benign				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Solid pseudopapillary tumour of the pancreas				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thymoma				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Uterine leiomyoma				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypertensive emergency				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Phlebitis				

subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Food allergy			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Cervical polyp			

subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ovarian cyst				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vaginal fistula				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vaginal haemorrhage				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Asthma				
subjects affected / exposed	2 / 49 (4.08%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Asthmatic crisis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Middle lobe syndrome				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nasal polyps				

subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary hypertension				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Status asthmaticus				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Endocrine test abnormal				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Arthropod bite				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bone contusion				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clavicle fracture				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Fall				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Femur fracture				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Head injury				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Incisional hernia				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ligament rupture				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Limb injury				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Multiple fractures				

subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Patella fracture				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural haemorrhage				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper limb fracture				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute coronary syndrome				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				

subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina unstable				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Congestive cardiomyopathy				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery insufficiency				

subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Supraventricular extrasystoles				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Diabetic neuropathy				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysarthria				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lumbosacral radiculopathy				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				

subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Hypochromic anaemia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Iron deficiency anaemia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain lower			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Barrett's oesophagus			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Colitis ulcerative				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer haemorrhage				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femoral hernia strangulated				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Irritable bowel syndrome				

subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal ulcer				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile duct stone				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis chronic				

subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatitis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Erythema nodosum				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pemphigoid				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rosacea				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urticaria papular				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Calculus urinary				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic kidney disease				

subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ureterolithiasis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Goitre				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperparathyroidism				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthritis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc protrusion				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Jaw cyst				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rotator cuff syndrome				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Anal abscess				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Erysipelas				

subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis salmonella				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection viral				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative abscess				

subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary sepsis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection viral				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinusitis bacterial				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection bacterial				
subjects affected / exposed	0 / 49 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urosepsis				

subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Obesity			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	SIROCCO/CALIMA - Benralizumab 30 mg q.4 weeks	SIROCCO/CALIMA - Benralizumab 30 mg q.8 weeks	ZONDA - Benralizumab 30 mg q.4 weeks
Total subjects affected by non-serious adverse events			
subjects affected / exposed	404 / 783 (51.60%)	392 / 793 (49.43%)	33 / 49 (67.35%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 783 (0.00%)	0 / 793 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Blood pressure increased			
subjects affected / exposed	4 / 783 (0.51%)	3 / 793 (0.38%)	1 / 49 (2.04%)
occurrences (all)	5	3	1
Vascular disorders			
Hypertension			
subjects affected / exposed	31 / 783 (3.96%)	28 / 793 (3.53%)	0 / 49 (0.00%)
occurrences (all)	32	32	0
Peripheral venous disease			

subjects affected / exposed	1 / 783 (0.13%)	3 / 793 (0.38%)	0 / 49 (0.00%)
occurrences (all)	1	3	0
Nervous system disorders			
Headache			
subjects affected / exposed	38 / 783 (4.85%)	40 / 793 (5.04%)	2 / 49 (4.08%)
occurrences (all)	54	54	2
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	26 / 783 (3.32%)	28 / 793 (3.53%)	3 / 49 (6.12%)
occurrences (all)	38	32	3
Injection site bruising			
subjects affected / exposed	0 / 783 (0.00%)	2 / 793 (0.25%)	0 / 49 (0.00%)
occurrences (all)	0	4	0
Non-cardiac chest pain			
subjects affected / exposed	2 / 783 (0.26%)	4 / 793 (0.50%)	0 / 49 (0.00%)
occurrences (all)	2	6	0
Oedema peripheral			
subjects affected / exposed	4 / 783 (0.51%)	6 / 793 (0.76%)	0 / 49 (0.00%)
occurrences (all)	4	7	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	13 / 783 (1.66%)	8 / 793 (1.01%)	2 / 49 (4.08%)
occurrences (all)	15	8	2
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	4 / 783 (0.51%)	8 / 793 (1.01%)	3 / 49 (6.12%)
occurrences (all)	5	8	3
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	12 / 783 (1.53%)	9 / 793 (1.13%)	1 / 49 (2.04%)
occurrences (all)	14	9	1
Gastritis			
subjects affected / exposed	6 / 783 (0.77%)	7 / 793 (0.88%)	2 / 49 (4.08%)
occurrences (all)	6	8	2
Large intestine polyp			

subjects affected / exposed	1 / 783 (0.13%)	1 / 793 (0.13%)	2 / 49 (4.08%)
occurrences (all)	1	1	2
Nausea			
subjects affected / exposed	10 / 783 (1.28%)	5 / 793 (0.63%)	2 / 49 (4.08%)
occurrences (all)	11	13	2
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	62 / 783 (7.92%)	53 / 793 (6.68%)	4 / 49 (8.16%)
occurrences (all)	98	72	4
Dyspnoea			
subjects affected / exposed	6 / 783 (0.77%)	9 / 793 (1.13%)	3 / 49 (6.12%)
occurrences (all)	6	9	3
Nasal congestion			
subjects affected / exposed	2 / 783 (0.26%)	12 / 793 (1.51%)	0 / 49 (0.00%)
occurrences (all)	2	12	0
Nasal polyps			
subjects affected / exposed	5 / 783 (0.64%)	4 / 793 (0.50%)	2 / 49 (4.08%)
occurrences (all)	6	4	2
Rhinitis allergic			
subjects affected / exposed	38 / 783 (4.85%)	22 / 793 (2.77%)	0 / 49 (0.00%)
occurrences (all)	43	31	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	11 / 783 (1.40%)	8 / 793 (1.01%)	3 / 49 (6.12%)
occurrences (all)	12	8	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	26 / 783 (3.32%)	20 / 793 (2.52%)	5 / 49 (10.20%)
occurrences (all)	32	20	5
Back pain			
subjects affected / exposed	24 / 783 (3.07%)	21 / 793 (2.65%)	2 / 49 (4.08%)
occurrences (all)	25	21	2
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	27 / 783 (3.45%)	44 / 793 (5.55%)	2 / 49 (4.08%)
occurrences (all)	45	57	5

Bronchitis			
subjects affected / exposed	49 / 783 (6.26%)	50 / 793 (6.31%)	3 / 49 (6.12%)
occurrences (all)	65	73	7
Bronchitis bacterial			
subjects affected / exposed	18 / 783 (2.30%)	15 / 793 (1.89%)	3 / 49 (6.12%)
occurrences (all)	23	21	3
Chronic sinusitis			
subjects affected / exposed	12 / 783 (1.53%)	10 / 793 (1.26%)	1 / 49 (2.04%)
occurrences (all)	13	17	1
Herpes zoster			
subjects affected / exposed	8 / 783 (1.02%)	2 / 793 (0.25%)	2 / 49 (4.08%)
occurrences (all)	8	2	2
Oral candidiasis			
subjects affected / exposed	14 / 783 (1.79%)	12 / 793 (1.51%)	1 / 49 (2.04%)
occurrences (all)	20	15	1
Respiratory tract infection viral			
subjects affected / exposed	8 / 783 (1.02%)	12 / 793 (1.51%)	2 / 49 (4.08%)
occurrences (all)	8	13	2
Sinusitis			
subjects affected / exposed	21 / 783 (2.68%)	18 / 793 (2.27%)	3 / 49 (6.12%)
occurrences (all)	23	22	3
Upper respiratory tract infection			
subjects affected / exposed	60 / 783 (7.66%)	55 / 793 (6.94%)	0 / 49 (0.00%)
occurrences (all)	94	81	0
Upper respiratory tract infection bacterial			
subjects affected / exposed	15 / 783 (1.92%)	22 / 793 (2.77%)	1 / 49 (2.04%)
occurrences (all)	17	27	1
Urinary tract infection			
subjects affected / exposed	14 / 783 (1.79%)	7 / 793 (0.88%)	0 / 49 (0.00%)
occurrences (all)	17	7	0
Viral upper respiratory tract infection			
subjects affected / exposed	121 / 783 (15.45%)	129 / 793 (16.27%)	14 / 49 (28.57%)
occurrences (all)	181	187	22

Non-serious adverse events	ZONDA - Benralizumab 30 mg q.8 weeks		

Total subjects affected by non-serious adverse events subjects affected / exposed	38 / 49 (77.55%)		
Investigations Blood creatinine increased subjects affected / exposed occurrences (all) Blood pressure increased subjects affected / exposed occurrences (all)	 2 / 49 (4.08%) 2 2 / 49 (4.08%) 2		
Vascular disorders Hypertension subjects affected / exposed occurrences (all) Peripheral venous disease subjects affected / exposed occurrences (all)	 2 / 49 (4.08%) 2 2 / 49 (4.08%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 4 / 49 (8.16%) 4		
General disorders and administration site conditions Influenza like illness subjects affected / exposed occurrences (all) Injection site bruising subjects affected / exposed occurrences (all) Non-cardiac chest pain subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all)	 1 / 49 (2.04%) 1 2 / 49 (4.08%) 2 2 / 49 (4.08%) 3 4 / 49 (8.16%) 6		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	 0 / 49 (0.00%) 0		

Eye disorders Conjunctivitis allergic subjects affected / exposed occurrences (all)	 0 / 49 (0.00%) 0		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Gastritis subjects affected / exposed occurrences (all) Large intestine polyp subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 2 / 49 (4.08%) 2 1 / 49 (2.04%) 1 1 / 49 (2.04%) 1 0 / 49 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Nasal polyps subjects affected / exposed occurrences (all) Rhinitis allergic subjects affected / exposed occurrences (all)	 7 / 49 (14.29%) 9 1 / 49 (2.04%) 1 2 / 49 (4.08%) 2 2 / 49 (4.08%) 2 2 / 49 (4.08%) 2		
Psychiatric disorders Insomnia			

subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	4		
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	4		
Bronchitis			
subjects affected / exposed	10 / 49 (20.41%)		
occurrences (all)	16		
Bronchitis bacterial			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	2		
Chronic sinusitis			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	7		
Herpes zoster			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Oral candidiasis			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	2		
Respiratory tract infection viral			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	4		
Upper respiratory tract infection			

subjects affected / exposed	7 / 49 (14.29%)		
occurrences (all)	8		
Upper respiratory tract infection bacterial			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	2		
Viral upper respiratory tract infection			
subjects affected / exposed	13 / 49 (26.53%)		
occurrences (all)	19		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 September 2015	Update study objectives; Remove requirement of continuing regular study visits after discontinuation of treatment; and other administrative changes.
13 January 2016	Add MELTEMI study as an extension of treatment study; Adjust unblinding language.
16 December 2016	Add Japanese interim analysis

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Patients in this study had to complete treatment in predecessor studies. Therefore selection bias may exist. Baseline is defined for this study’s entry value, not all values are prior to active treatment due to some patients being treated previously.

Notes: