Clinical trial results:
A Phase 2a, Double-blind, Placebo-controlled Study to Evaluate the Efficacy of MEDI-563 in Subjects with Moderate-to-severe Chronic Obstructive Pulmonary Disease and Sputum Eosinophilia

Summary

EudraCT number	2010-020127-52
Trial protocol	GB ES DE DK
Global end of trial date	11 July 2013

Results information

Result version number	v1 (current)
This version publication date	20 October 2016
First version publication date	20 October 2016

Trial information

Trial identification

Sponsor protocol code	MI-CP196

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01227278
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	MedImmune, LLC.
Sponsor organisation address	Milstein Building, Granta Park, Cambridge, CB21 6GH, United Kingdom,
Public contact	Rene van der Merwe, MBChB/Senior Director, Clinical Development, MedImmune, LLC., +1 3013980000, vandermerwer@medimmune.com
Scientific contact	Rene van der Merwe, MBChB/Senior Director, Clinical Development, MedImmune, LLC., +1 3013980000, vandermerwer@medimmune.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 July 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the effect of multiple subcutaneous (SC) doses of benralizumab on the rate of moderate or severe acute exacerbations of chronic obstructive pulmonary disease (AECOPD) in adult participants with moderate-to severe chronic obstructive pulmonary disease (COPD) who exhibited eosinophilia [greater than or equal to 9 (>=) 3.0 percent (%) sputum eosinophilia in the previous 12 months or at screening] in sputum compared to placebo.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Participating participant signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 November 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Poland: 29
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	United States: 22
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	Spain: 7
Worldwide total number of subjects	101
EEA total number of subjects	65

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	55
From 65 to 84 years	45
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 421 participants were screened and 101 participants were randomized into the study.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants reecieved placebo matched to benralizumab (MEDI-563) injection subcutaneously every 4 weeks for the first 3 doses and then every 8 weeks for the next 5 doses (Day 1, 29, 57, 113, 169, 225, 281 and 337).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo matched to benralizumab (MEDI-563) injection subcutaneously every 4 weeks for the first 3 doses and then every 8 weeks for the next 5 doses (Day 1, 29, 57, 113, 169, 225, 281 and 337).

Arm title	Benralizumab 100 mg

Arm description:

Particpants received Benralizumab (MEDI-563) 100 milligram (mg) injection subcutaneously every 4 weeks for the first 3 doses and then every 8 weeks for the next 5 doses (Day 1, 29, 57, 113, 169, 225, 281 and 337).

Arm type	Experimental
Investigational medicinal product name	Benralizumab
Investigational medicinal product code	MEDI-563
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Benralizumab (MEDI-563) 100 mg injection subcutaneously every 4 weeks for the first 3 doses and then every 8 weeks for the next 5 doses (Day 1, 29, 57, 113, 169, 225, 281 and 337).

Number of subjects in period 1	Placebo	Benralizumab 100 mg
Started	50	51
Completed	45	43
Not completed	5	8
Adverse event, serious fatal	-	2
Consent withdrawn by subject	4	4
Unspecified	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants reecieved placebo matched to benralizumab (MEDI-563) injection subcutaneously every 4 weeks for the first 3 doses and then every 8 weeks for the next 5 doses (Day 1, 29, 57, 113, 169, 225, 281 and 337).	
Reporting group title	Benralizumab 100 mg
Reporting group description:	
Particpants received Benralizumab (MEDI-563) 100 milligram (mg) injection subcutaneously every 4 weeks for the first 3 doses and then every 8 weeks for the next 5 doses (Day 1, 29, 57, 113, 169, 225, 281 and 337).	

Reporting group values	Placebo	Benralizumab 100 mg	Total
Number of subjects	50	51	101
Age categorical Units: Subjects			
Adults (18-64 years)	25	30	55
Elderly (From 65-84 years)	24	21	45
Elderly 85 years and over	1	0	1
Age Continuous | Units: years			
arithmetic mean	64.6	62.9	
standard deviation	± 7.5	± 8.2	-
Gender, Male/Female Units: participants			
Female	21	16	37
Male	29	35	64

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants reecieved placebo matched to benralizumab (MEDI-563) injection subcutaneously every 4 weeks for the first 3 doses and then every 8 weeks for the next 5 doses (Day 1, 29, 57, 113, 169, 225, 281 and 337).	
Reporting group title	Benralizumab 100 mg
Reporting group description:	
Particpants received Benralizumab (MEDI-563) 100 milligram (mg) injection subcutaneously every 4 weeks for the first 3 doses and then every 8 weeks for the next 5 doses (Day 1, 29, 57, 113, 169, 225, 281 and 337).	

Primary: Annualized Incidence Rate of Moderate or Severe Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD)

End point title	Annualized Incidence Rate of Moderate or Severe Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD)
End point description:	
An AECOPD is defined as worsening of two or more major symptoms or one major and one minor symptom for two or more consecutive days. Annualized Incidence Rate of Moderate or Severe AECOPD was assessed based on AECOPD data up to Day 393 (Rate = total number of moderate or severe AECOPD in each group/total person-year follow-up in each group). The severity of an exacerbation of COPD is defined as: a) Mild exacerbations, which require treatment with an increase in usual therapy, example, increase use of short acting bronchodilators, b) Moderate exacerbations which require treatment with systemic corticosteroids, and or antibiotics and c) Severe exacerbations which require hospitalization. The per protocol (PP) population included all participants who had no major protocol violations, received at least 6 of the 8 total doses of investigational product, and completed the study through Day 393.	
End point type	Primary
End point timeframe:	
Day 1 up to 393	

End point values	Placebo	Benralizumab 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: AECOPD events/person-year				
number (confidence interval 95%)	0.92 (0.67 to 1.25)	0.95 (0.68 to 1.29)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Benralizumab 100 mg

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.941 [2]
Method	Van Elteren Test
Parameter estimate	Rate ratio
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.58

Notes:

[1] - 95 percent (%) confidence interval (CI) for rate ratio was based on normal approximation assuming rate with Poisson distribution.
[2] - Day 1 to 393: Van Elteren test was used to compare the two arms.

Secondary: Number of Participants Reporting Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)

End point title	Number of Participants Reporting Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)

End point description:

An adverse event (AE) was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent are events between administration of study drug and up to Day 561 that were absent before treatment or that worsened relative to pre-treatment state. TEAEs reported below included both SAEs and non-serious AEs. The safety population included all participants who received at least one dose of investigational drug.

End point type	Secondary

End point timeframe:

Day 1 up to 561

End point values	Placebo	Benralizumab 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: participants				
TEAEs	41	45		
TESAEs	9	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Hospitalized due to Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD)

End point title	Number of Participants Hospitalized due to Acute Exacerbations

	of Chronic Obstructive Pulmonary Disease (AECOPD)

End point description:

An AECOPD is defined as worsening of two or more major symptoms or one major and one minor symptom for two or more consecutive days. The PP population included all participants who had no major protocol violations, received at least 6 of the 8 total doses of investigational product and completed the study through Day 393.

End point type	Secondary

End point timeframe:

Day 1 up to 393

End point values	Placebo	Benralizumab 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: participants	5	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Hospitalized due to Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD)

End point title	Percentage of Participants Hospitalized due to Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD)

End point description:

An AECOPD is defined as worsening of two or more major symptoms or one major and one minor symptom for two or more consecutive days. The PP population included all participants who had no major protocol violations, received at least 6 of the 8 total doses of investigational product, and completed the study through Day 393.

End point type	Secondary

End point timeframe:

Day 1 up to 393

End point values	Placebo	Benralizumab 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: percentage of participants				
number (not applicable)	11.9	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Annual Incidence Rate of Hospitalization due to Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD)

End point title	Annual Incidence Rate of Hospitalization due to Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD)

End point description:

An AECOPD is defined as worsening of two or more major symptoms or one major and one minor symptom for two or more consecutive days. Annualized Incidence Rate of hospitalization due to AECOPD was calculated as Rate = total number of hospitalizations/ total person years. The PP population included all participants who had no major protocol violations, received at least 6 of the 8 total doses of investigational product, and completed the study through Day 393.

End point type	Secondary

End point timeframe:

Day 1 up to 393

End point values	Placebo	Benralizumab 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: hospitalizations/person-year				
number (confidence interval 95%)	0.11 (0.05 to 0.26)	0.05 (0.01 to 0.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in COPD-Specific Saint George's Respiratory Questionnaire (SGRQ-C) Total and Domain Scores at Day 393

End point title	Change from Baseline in COPD-Specific Saint George's Respiratory Questionnaire (SGRQ-C) Total and Domain Scores at Day 393

End point description:

The SGRQ is a health related quality of life questionnaire consisting of 40 items in three domains: symptoms (respiratory symptoms and severity), activity (activities that cause or are limited by breathlessness) and impacts (social functioning and psychological disturbances due to airway disease). Each question's response has a unique empirically derived weight where lowest possible weight is zero and the highest is 100. The total score and domain score are derived from the relevant items and converted to a score of 0 to 100 with a higher score indicating poorer health status. The PP population included all participants who had no major protocol violations, received at least 6 of the 8 total doses of investigational product, and completed the study through Day 393. Here, 'n' signifies those participants evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Day 393

End point values	Placebo	Benralizumab 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: units on scale				
arithmetic mean (standard deviation)				
Baseline: Total Score (n=42, 40)	48.04 (± 19.14)	51.75 (± 20.45)		
Change at Day 393: Total Score (n=42, 37)	-4.43 (± 11.71)	-5.51 (± 16.64)		
Baseline: Symptoms (n=42, 40)	64.59 (± 24.38)	67.18 (± 21.47)		
Change at Day 393: Symptoms (n=42, 37)	-3.19 (± 17.44)	-9.02 (± 21.27)		
Baseline: Activity (n=42, 40)	58.85 (± 23.22)	61.45 (± 25.53)		
Change at Day 393: Activity (n=42, 37)	-5.65 (± 14.85)	-4.37 (± 24.89)		
Baseline: Impact (n=42, 40)	35.94 (± 18.95)	40.69 (± 22.49)		
Change at Day 393: Impact (n=42, 37)	-4.16 (± 14.62)	-4.95 (± 16.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Improvement in COPD-Specific Saint George’s Respiratory Questionnaire (SGRQ-C) Total Score

End point title	Percentage of Participants with Improvement in COPD-Specific Saint George’s Respiratory Questionnaire (SGRQ-C) Total Score

End point description:

SGRQ is a health related quality of life questionnaire consisting of 40 items in three domains: symptoms (respiratory symptoms and severity) activity (activities that cause or are limited by breathlessness) and impacts (social functioning and psychological disturbances due to airway disease). Each question’s response has a unique empirically derived weight where lowest possible weight is zero and the highest is 100. The total score and domain score were derived from the relevant items and converted to a score of 0 to 100 with a higher score indicating poorer health status. Percentage of participants with 4-point, 8-point and 12-point change from baseline in COPD-Specific Saint George’s Respiratory Questionnaire (SGRQ-C) total score were observed. The PP population was analysed. Here, 'n' signifies those participants evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Day 393

End point values	Placebo	Benralizumab 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: percentage of participants				
number (not applicable)				
Day 393: Total: 4-point change (n=42, 37)	59.5	54.1		

Day 393: 8-point change (n=42, 37)	38.1	40.5		
Day 393: Total: 12-point change (n=42, 37)	21.4	24.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Chronic Respiratory Questionnaire Self-Administered Standardized Format (CRQ-SAS) Domain scores at Day 393

End point title	Change from Baseline in Chronic Respiratory Questionnaire Self-Administered Standardized Format (CRQ-SAS) Domain scores at Day 393

End point description:

CRQ-SAS is a self-administered questionnaire which consist of 20 items across four domains: dyspnea (5 items), fatigue (4 items), emotional function (7 items), and mastery (4 items). Participants rated their experience on a 7-point scale in response to each item ranging from 1 (maximum impairment) to 7 (no impairment). Individual items were equally weighted, and domain scores were calculated as the mean of all items within each domain; domain score range: 1 (maximum impairment) to 7 (no impairment). The PP population included all participants who had no major protocol violations, received at least 6 of the 8 total doses of investigational product, and completed the study through Day 393. Here, 'n' signifies those participants evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Day 393

End point values	Placebo	Benralizumab 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: units on scale				
arithmetic mean (standard deviation)				
Baseline: Dyspnea (n=42, 40)	4.97 (± 1.45)	4.74 (± 1.32)		
Change at Day 393: Dyspnea (n=42, 37)	-0.08 (± 1.29)	0.09 (± 1)		
Baseline: Fatigue (n=42, 40)	4.38 (± 1.26)	3.96 (± 1.4)		
Change at Day 393: Fatigue (n=42, 37)	0.11 (± 0.94)	0.11 (± 1.15)		
Baseline: Emotional function (n=42, 40)	4.84 (± 1.24)	4.72 (± 1.17)		
Change at Day 393: Emotional function (n=42, 37)	0.18 (± 0.98)	0.08 (± 1.18)		
Baseline: Mastery (n=42, 40)	4.89 (± 1.5)	4.67 (± 1.4)		
Change at Day 393: Mastery (n=42, 37)	0.24 (± 1.12)	0.28 (± 1.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a 0.5-Point Improvement in Chronic Respiratory Questionnaire Self-administered Standardized Format (CRQ-SAS) Domain scores at Day 393

End point title	Percentage of Participants With a 0.5-Point Improvement in Chronic Respiratory Questionnaire Self-administered Standardized Format (CRQ-SAS) Domain scores at Day 393

End point description:

The CRQ-SAS is a self-administered questionnaire which consist of 20 items across four domains: dyspnea (5 items), fatigue (4 items), emotional function (7 items), and mastery (4 items). Participants rated their experience on a 7-point scale in response to each item ranging from 1 (maximum impairment) to 7 (no impairment). Individual items were equally weighted, and domain scores were calculated as the mean of all items within each domain; domain score range: 1 (maximum impairment) to 7 (no impairment). Participants with 0.5 point improvement from baseline in the domain scores were observed. The PP population included all participants who had no major protocol violations, received at least 6 of the 8 total doses of investigational product, and completed the study through Day 393. Here, 'n' signifies those participants evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Day 393

End point values	Placebo	Benralizumab 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: percentage of participants				
number (not applicable)				
Day 393: Dyspnea (n=42, 37)	28.6	32.4		
Day 393: Fatigue (n=42, 37)	35.7	35.1		
Day 393: Emotional function (n=42, 37)	35.7	27		
Day 393: Mastery (n=42, 37)	47.6	37.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Body Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity (BODE) Scores at Day 393

End point title	Change from Baseline in Body Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity (BODE) Scores at Day 393

End point description:

The BODE index is a multi-dimension COPD grading system that incorporates body-mass index (B), degree of airflow obstruction (O), dyspnea (D), and exercise capacity (E) as measured by the modified medical research council (MMRC) dyspnea scale and the 6-minute walk test. The MMRC dyspnea scale is a 5-point scale that measures the level of dyspnea (trouble breathing) experienced by participants where score range is 0 (none) to 4 (very severe). BODE score is derived into a score range of 0 (healthy) to 10 (severe COPD). The PP population included all participants who had no major protocol violations, received at least 6 of the 8 total doses of investigational product, and completed the study through Day 393. Here, 'n' signifies those participants evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:
Baseline, Day 393

End point values	Placebo	Benralizumab 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: units on scale				
arithmetic mean (standard deviation)				
Baseline (n=40, 39)	2.8 (± 2)	2.9 (± 1.8)		
Change at Day 393 (n=37, 32)	-0.1 (± 1.4)	-0.5 (± 1.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to 561

Adverse event reporting additional description:

The safety population included all participants who received at least one dose of investigational drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Benralizumab 100 mg

Reporting group description:

Benralizumab (MEDI-563) 100 milligram (mg) injection subcutaneously every 4 weeks for the first 3 doses and then every 8 weeks for the next 5 doses (Day 1, 29, 57, 113, 169, 225, 281 and 337).

Reporting group title	Placebo

Reporting group description:

Placebo matched to benralizumab (MEDI-563) injection subcutaneously every 4 weeks for the first 3 doses and then every 8 weeks for the next 5 doses (Day 1, 29, 57, 113, 169, 225, 281 and 337).

Serious adverse events	Benralizumab 100 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 51 (27.45%)	9 / 50 (18.00%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-hodgkin's lymphoma			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			

subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Presyncope			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	6 / 51 (11.76%)	6 / 50 (12.00%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			

subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal abscess			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis syndrome			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Benralizumab 100 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 51 (86.27%)	41 / 50 (82.00%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	2 / 51 (3.92%)	1 / 50 (2.00%)	
occurrences (all)	2	1	
Hypertension			

subjects affected / exposed	1 / 51 (1.96%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Aortic arteriosclerosis			
subjects affected / exposed	0 / 51 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Hypotension			
subjects affected / exposed	2 / 51 (3.92%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 51 (3.92%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Injection site erythema			
subjects affected / exposed	3 / 51 (5.88%)	0 / 50 (0.00%)	
occurrences (all)	3	0	
Injection site inflammation			
subjects affected / exposed	2 / 51 (3.92%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Injection site pain			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Injection site reaction			
subjects affected / exposed	3 / 51 (5.88%)	0 / 50 (0.00%)	
occurrences (all)	3	0	
Oedema peripheral			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed	3 / 51 (5.88%)	0 / 50 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	26 / 51 (50.98%)	25 / 50 (50.00%)	
occurrences (all)	53	62	
Cough			

subjects affected / exposed	1 / 51 (1.96%)	4 / 50 (8.00%)	
occurrences (all)	1	4	
Dyspnoea			
subjects affected / exposed	2 / 51 (3.92%)	5 / 50 (10.00%)	
occurrences (all)	2	5	
Dyspnoea exertional			
subjects affected / exposed	2 / 51 (3.92%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Epistaxis			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Rhinitis allergic			
subjects affected / exposed	0 / 51 (0.00%)	3 / 50 (6.00%)	
occurrences (all)	0	3	
Oropharyngeal pain			
subjects affected / exposed	0 / 51 (0.00%)	4 / 50 (8.00%)	
occurrences (all)	0	4	
Investigations			
C-reactive protein increased			
subjects affected / exposed	2 / 51 (3.92%)	1 / 50 (2.00%)	
occurrences (all)	2	1	
Breath sounds abnormal			
subjects affected / exposed	0 / 51 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	2 / 51 (3.92%)	2 / 50 (4.00%)	
occurrences (all)	2	2	
Fall			
subjects affected / exposed	3 / 51 (5.88%)	1 / 50 (2.00%)	
occurrences (all)	3	1	
Contusion			
subjects affected / exposed	3 / 51 (5.88%)	0 / 50 (0.00%)	
occurrences (all)	3	0	
Post procedural complication			

subjects affected / exposed	2 / 51 (3.92%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	2 / 51 (3.92%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 51 (7.84%)	3 / 50 (6.00%)	
occurrences (all)	7	3	
Dizziness			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Paraesthesia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Sciatica			
subjects affected / exposed	2 / 51 (3.92%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	0 / 51 (0.00%)	4 / 50 (8.00%)	
occurrences (all)	0	4	
Constipation			
subjects affected / exposed	2 / 51 (3.92%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Abdominal pain upper			
subjects affected / exposed	0 / 51 (0.00%)	4 / 50 (8.00%)	
occurrences (all)	0	4	
Gastrooesophageal reflux disease			

subjects affected / exposed	2 / 51 (3.92%)	3 / 50 (6.00%)	
occurrences (all)	2	3	
Nausea			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 51 (3.92%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 51 (3.92%)	0 / 50 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Back pain			
subjects affected / exposed	3 / 51 (5.88%)	1 / 50 (2.00%)	
occurrences (all)	3	1	
Joint swelling			
subjects affected / exposed	1 / 51 (1.96%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 51 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Musculoskeletal pain			
subjects affected / exposed	0 / 51 (0.00%)	3 / 50 (6.00%)	
occurrences (all)	0	3	
Muscle spasms			
subjects affected / exposed	3 / 51 (5.88%)	0 / 50 (0.00%)	
occurrences (all)	3	0	
Myalgia			
subjects affected / exposed	1 / 51 (1.96%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Pain in extremity			

subjects affected / exposed	3 / 51 (5.88%)	0 / 50 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Gastroenteritis			
subjects affected / exposed	2 / 51 (3.92%)	1 / 50 (2.00%)	
occurrences (all)	3	1	
Cystitis			
subjects affected / exposed	1 / 51 (1.96%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Bronchitis			
subjects affected / exposed	3 / 51 (5.88%)	3 / 50 (6.00%)	
occurrences (all)	3	3	
Nasopharyngitis			
subjects affected / exposed	5 / 51 (9.80%)	11 / 50 (22.00%)	
occurrences (all)	8	13	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	1	3	
Gastroenteritis viral			
subjects affected / exposed	2 / 51 (3.92%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Oral candidiasis			
subjects affected / exposed	0 / 51 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Pharyngitis			
subjects affected / exposed	4 / 51 (7.84%)	1 / 50 (2.00%)	
occurrences (all)	4	1	
Pneumonia			
subjects affected / exposed	2 / 51 (3.92%)	2 / 50 (4.00%)	
occurrences (all)	2	2	
Rhinitis			

subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	2	1	
Sinusitis			
subjects affected / exposed	3 / 51 (5.88%)	4 / 50 (8.00%)	
occurrences (all)	3	4	
Upper respiratory tract infection			
subjects affected / exposed	5 / 51 (9.80%)	1 / 50 (2.00%)	
occurrences (all)	6	1	
Urinary tract infection			
subjects affected / exposed	3 / 51 (5.88%)	1 / 50 (2.00%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2011	- Study stopping criteria were amended.-Inclusion and exclusion criteria were revised.-Rescreening of participants was updated to 2 re-screenings for who had screen failed due to Hepatitis A and moderate-to-severe exacerbation prior to or after starting the 28-day run-in period.-Unblinding due to known effects of Benralizumab was revised.- Anticipated number of screened participants were removed from treatment regimens.- Treatment regimens and maintenance therapy were added.- Allowed concomitant medication during the study was revised.- Day28 was removed from Schedule of study procedures.- Text was updated in Schedule of study procedures and in Schedule of Participant Evaluations.-Office Spirometry Pre- and Post-bronchodilator was revised.- Wheeze was removed from visual analogue scales (VAS).- Patient-Reported Outcomes Questionnaire (PRO-Q) was added.- Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD) Inpatient assessment was added.
15 February 2011	-Participants with a history of an untreated systemic helminth parasitic infestation were excluded. - Stool sampling added to Clinical Laboratory Tests. - Rescreening of participants was updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported