Clinical trial results:
MEA115588 A randomised, double-blind, double-dummy, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of mepolizumab adjunctive therapy in subjects with severe uncontrolled refractory asthma

Summary

EudraCT number	2012-001251-40
Trial protocol	BE GB DE ES IT Outside EU/EEA
Global end of trial date	18 January 2014

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	04 June 2015

Trial information

Trial identification

Sponsor protocol code	MEA115588

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000069-PIP02-10
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	10 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of mepolizumab 75 mg intravenous (i.v.) or 100 mg subcutaneous (SC) every 4 weeks versus placebo on the frequency of clinically significant exacerbations in adult and adolescent subjects with severe, uncontrolled, refractory asthma

Protection of trial subjects:

Numbing cream or spray was permitted at the site of injection and rescue medications (salbuterol/albuterol) are available to the participant throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 October 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	Belgium: 22
Country: Number of subjects enrolled	France: 72
Country: Number of subjects enrolled	Germany: 78
Country: Number of subjects enrolled	Italy: 58
Country: Number of subjects enrolled	Canada: 35
Country: Number of subjects enrolled	United States: 68
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Russian Federation: 17
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Argentina: 43
Country: Number of subjects enrolled	Japan: 50
Country: Number of subjects enrolled	Korea, Republic of: 45
Country: Number of subjects enrolled	Ukraine: 18
Country: Number of subjects enrolled	Chile: 23
Worldwide total number of subjects	580
EEA total number of subjects	273

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)	25
Adults (18-64 years)	474
From 65 to 84 years	81
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Par. who met the eligibility criteria at screening, entered the Run-in period for a minimum of 1 week and a maximum of 6 weeks. Par. who received all 8 doses and met the eligibility criteria were offered the opportunity to participate in an open label extension (OLE) study. Par. not entering the OLE study completed the Follow-up Visit.

Pre-assignment

Screening details:

A total of 802 participants (par.) were enrolled; 82 were Screen failures; 140 were Run-in failures; 580 were randomized, of which 576 received at least 1 dose of study drug.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo intravenously (IV) plus placebo subcutaneously (SC) every 4 weeks (for a total of 8 doses), with the last dose at Week 28. The SC dose and the IV dose were administered into separate arms. A topical anaesthetic was permitted at the injection site to minimize discomfort, as needed. Rescue personnel and rescue medications (salbutamol/albuterol) /equipment were available throughout the study.

Arm type	Placebo
Investigational medicinal product name	Placebo (Normal Saline)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

IV and SC q4weeks

Arm title	Mepolizumab 75 mg IV

Arm description:

Participants received mepolizumab 75 milligrams (mg) IV plus placebo SC every 4 weeks (for a total of 8 doses), with the last dose at Week 28. The SC dose and the IV dose were administered into separate arms. A topical anaesthetic was permitted at the injection site to minimize discomfort, as needed. Rescue personnel and rescue medications (salbutamol/albuterol) /equipment were available throughout the study.

Arm type	Experimental
Investigational medicinal product name	Mepolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

75mg IV q4weeks x 8doses plus NS SC

Arm title	Mepolizumab 100 mg SC

Arm description:

Participants received placebo IV plus mepolizumab 100 mg SC every 4 weeks (for a total of 8 doses), with the last dose at Week 28. The SC dose and the IV dose were administered into separate arms. A topical anaesthetic was permitted at the injection site to minimize discomfort, as needed. Rescue personnel and rescue medications (salbutamol/albuterol) /equipment were available throughout the study.

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

Dosage and administration details:

100mg SC q4 weeks x 8 doses plus NS IV

Number of subjects in period 1[1]	Placebo	Mepolizumab 75 mg IV	Mepolizumab 100 mg SC
Started	191	191	194
Completed	179	175	185
Not completed	12	16	9
Adverse event, serious fatal	1	-	-
Physician decision	2	1	-
Consent withdrawn by subject	5	9	4
Adverse event, non-fatal	3	-	1
Lost to follow-up	-	2	2
Lack of efficacy	1	1	2
Protocol deviation	-	3	-

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: 580 participants were randomized, of which 576 received at least 1 dose of study drug. The baseline period represents the participants that received at least 1 dose of study drug.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo

Reporting group description:

Participants received placebo intravenously (IV) plus placebo subcutaneously (SC) every 4 weeks (for a total of 8 doses), with the last dose at Week 28. The SC dose and the IV dose were administered into separate arms. A topical anaesthetic was permitted at the injection site to minimize discomfort, as needed. Rescue personnel and rescue medications (salbutamol/albuterol) /equipment were available throughout the study.

Reporting group title	Mepolizumab 75 mg IV

Reporting group description:

Participants received mepolizumab 75 milligrams (mg) IV plus placebo SC every 4 weeks (for a total of 8 doses), with the last dose at Week 28. The SC dose and the IV dose were administered into separate arms. A topical anaesthetic was permitted at the injection site to minimize discomfort, as needed. Rescue personnel and rescue medications (salbutamol/albuterol) /equipment were available throughout the study.

Reporting group title	Mepolizumab 100 mg SC

Reporting group description:

Participants received placebo IV plus mepolizumab 100 mg SC every 4 weeks (for a total of 8 doses), with the last dose at Week 28. The SC dose and the IV dose were administered into separate arms. A topical anaesthetic was permitted at the injection site to minimize discomfort, as needed. Rescue personnel and rescue medications (salbutamol/albuterol) /equipment were available throughout the study.

Reporting group values	Placebo	Mepolizumab 75 mg IV	Mepolizumab 100 mg SC
Number of subjects	191	191	194
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	49.2	50	51.2
standard deviation	± 14.26	± 14.03	± 14.55
Gender categorical Units: Subjects			
Female	107	106	116
Male	84	85	78
Race Units: Subjects			
African American/African Heritage	3	6	7
American Indian or Alaskan Native	0	0	1
Asian - Central/South Asian Heritage	1	1	0
Asian - East Asian Heritage	15	15	15
Asian - Japanese Heritage	18	17	17
Asian - South East Asian Heritage	4	0	2
White - Arabic/North African Heritage	4	3	4
White - White/Caucasian/European Heritage	144	148	148
Mixed Race	2	1	0

Reporting group values	Total		
Number of subjects	576		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	329		
Male	247		
Race Units: Subjects			
African American/African Heritage	16		
American Indian or Alaskan Native	1		
Asian - Central/South Asian Heritage	2		
Asian - East Asian Heritage	45		
Asian - Japanese Heritage	52		
Asian - South East Asian Heritage	6		
White - Arabic/North African Heritage	11		
White - White/Caucasian/European Heritage	440		
Mixed Race	3		

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo intravenously (IV) plus placebo subcutaneously (SC) every 4 weeks (for a total of 8 doses), with the last dose at Week 28. The SC dose and the IV dose were administered into separate arms. A topical anaesthetic was permitted at the injection site to minimize discomfort, as needed. Rescue personnel and rescue medications (salbutamol/albuterol) /equipment were available throughout the study.

Reporting group title	Mepolizumab 75 mg IV

Reporting group description:

Participants received mepolizumab 75 milligrams (mg) IV plus placebo SC every 4 weeks (for a total of 8 doses), with the last dose at Week 28. The SC dose and the IV dose were administered into separate arms. A topical anaesthetic was permitted at the injection site to minimize discomfort, as needed. Rescue personnel and rescue medications (salbutamol/albuterol) /equipment were available throughout the study.

Reporting group title	Mepolizumab 100 mg SC

Reporting group description:

Participants received placebo IV plus mepolizumab 100 mg SC every 4 weeks (for a total of 8 doses), with the last dose at Week 28. The SC dose and the IV dose were administered into separate arms. A topical anaesthetic was permitted at the injection site to minimize discomfort, as needed. Rescue personnel and rescue medications (salbutamol/albuterol) /equipment were available throughout the study.

Primary: Number of clinically significant exacerbations of asthma per year

End point title	Number of clinically significant exacerbations of asthma per year

End point description:

Clinically significant exacerbations of asthma are defined as worsening of asthma which required use of systemic corticosteroids (IV or oral steroid like prednisone, for at least 3 days or a single intramuscular (IM) corticosteroid (CS) dose is required. For maintenance of systemic corticosteroids, at least double the existing maintenance dose for at least 3 days was required) and/or hospitalization and/or emergency department (ED) visits. The frequency of clinically significant exacerbations of asthma over the 32-week treatment period is expressed as the number of exacerbations per year. Analysis of the number of exacerbations performed using a negative binomial model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable) and baseline % predicted FEV1, and with logarithm of time on treatment as an offset variable.

End point type	Primary

End point timeframe:

From randomization (Week 0) to Week 32 or if Early Withdrawal (EW) 4 weeks post last dose

End point values	Placebo	Mepolizumab 75 mg IV	Mepolizumab 100 mg SC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191[1]	191[2]	194[3]	
Units: Number of exacerbations per year				
number (not applicable)	1.74	0.93	0.83	

Notes:

[1] - Modified ITT Population: all participants who were randomized and who received >1 dose of treatment.
[2] - Modified ITT Population: all participants who were randomized and who received >1 dose of treatment.
[3] - Modified ITT Population: all participants who were randomized and who received >1 dose of treatment.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo v Mepolizumab 75 mg IV
Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.001 [5]
Method	Negative binomial model
Parameter estimate	Rate Ratio
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.72

Notes:

[4] - Number of exacerbations per year in the mepolizumab 75mg IV arm divided by the number of exacerbations per year in the placebo arm.
[5] - Hochberg procedure with a gamma parameter of 1 used for multiplicity adjustment.

Statistical analysis title	Analysis 2
Comparison groups	Placebo v Mepolizumab 100 mg SC
Number of subjects included in analysis	385
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.001 [7]
Method	Negative binomial model
Parameter estimate	Rate Ratio
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.64

Notes:

[6] - Number of exacerbations per year in the mepolizumab 100 mg SC arm divided by the number of exacerbations per year in the placebo arm.
[7] - Hochberg procedure with a gamma parameter of 1 used for multiplicity adjustment.

Secondary: Number of clinically significant exacerbations requiring hospitalization (including intubation and admittance to an intensive care unit [ICU]) or ED visits per year

End point title	Number of clinically significant exacerbations requiring hospitalization (including intubation and admittance to an intensive care unit [ICU]) or ED visits per year

End point description:

Clinically significant exacerbations of asthma are defined as worsening of asthma which required use of systemic corticosteroids (IV or oral steroid like prednisone, for at least 3 days or a single intramuscular (IM) corticosteroid (CS) dose is required. For maintenance of systemic corticosteroids, at least double the existing maintenance dose for at least 3 days was required) and/or hospitalization and/or emergency department (ED) visits. The frequency of clinically significant exacerbations of asthma over the 32-week treatment period is expressed as the number of exacerbations per year. Analysis of the number of exacerbations performed using a negative binomial model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable) and baseline % predicted FEV1, and with logarithm of time on treatment as an offset variable.

End point type	Secondary

End point timeframe:

From randomization (Week 0) to Week 32 or if Early Withdrawal (EW) 4 weeks post last dose

End point values	Placebo	Mepolizumab 75 mg IV	Mepolizumab 100 mg SC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191[8]	191[9]	194[10]	
Units: Number of exacerbations per year				
number (not applicable)	0.2	0.14	0.08	

Notes:

[8] - ITT Population

[9] - ITT Population

[10] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of clinically significant exacerbations requiring hospitalization (including intubation and admittance to an ICU) per year

End point title	Number of clinically significant exacerbations requiring hospitalization (including intubation and admittance to an ICU) per year

End point description:

Clinically significant exacerbations of asthma is defined as worsening of asthma which required use of systemic corticosteroids (IV or oral steroid like prednisone, for at least 3 days or a single intramuscular (IM) corticosteroid (CS) dose is required. For maintenance of systemic corticosteroids, at least double the existing maintenance dose for at least 3 days was required) and/or hospitalization. The frequency of clinically significant exacerbations of asthma over the 32-week treatment period is expressed as the number of exacerbations per year. Analysis of the number of exacerbations performed using a negative binomial model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable) and baseline % predicted FEV1, and with logarithm of time on treatment as an offset variable.

End point type	Secondary

End point timeframe:

From randomization (Week 0) to Week 32 or if Early Withdrawal (EW) 4 weeks post last dose

End point values	Placebo	Mepolizumab 75 mg IV	Mepolizumab 100 mg SC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191[11]	191[12]	194[13]	
Units: Number of exacerbations per year				
number (not applicable)	0.1	0.06	0.03	

Notes:

[11] - ITT Population

[12] - ITT Population

[13] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in clinic pre-bronchodilator forced expiratory volume in 1 second (FEV1) at Week 32

End point title	Mean change from Baseline in clinic pre-bronchodilator forced expiratory volume in 1 second (FEV1) at Week 32

End point description:

FEV1 is defined as the volume of air expelled from the lungs in 1 second. Pre-bronchodilator FEV1 measurements were taken by spirometry. The change from Baseline is defined as the difference between the value of the endpoint at the time point of interest and the baseline value. Analysis performed using mixed model repeated measures with covariates of baseline, region, baseline maintenance OCS therapy (OCS vs. no OCS), exacerbations in the year prior to the study (as an ordinal variable), treatment and visit, plus interaction terms for visit by baseline and visit by treatment group.

End point type	Secondary

End point timeframe:

Baseline, Week 32

End point values	Placebo	Mepolizumab 75 mg IV	Mepolizumab 100 mg SC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	189[14]	188[15]	192[16]	
Units: Milliliters (mL)				
least squares mean (standard error)	86 (± 31.4)	186 (± 31.5)	183 (± 31.1)	

Notes:

[14] - ITT Population

[15] - ITT Population

[16] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in the St. George’s Respiratory Questionnaire total score at Week 32

End point title	Mean change from Baseline in the St. George’s Respiratory Questionnaire total score at Week 32

End point description:

The St. George’s Respiratory Questionnaire is an established instrument, comprising 50 questions, evaluating symptoms, activity, and impacts; to measure Quality of Life in participants with diseases of

airway obstruction and to elicit the participant's opinion of his/her health. The lowest possible value is zero and the highest possible value is 100. The higher values correspond to greater impairment in quality of life. The questionnaire was administered at Baseline (Visit 2) and at the Exit Visit (approximately 4 weeks after the last dose of study treatment). The change from baseline is defined as the difference between the value of the endpoint at the time point of interest and the baseline value. Analysis performed using analysis of covariance with covariates of baseline, region, baseline maintenance OCS therapy (OCS vs. no OCS), exacerbations in the year prior to the study (as an ordinal variable), baseline % predicted FEV1, and treatment.

End point type	Secondary

End point timeframe:

Baseline, Week 32

End point values	Placebo	Mepolizumab 75 mg IV	Mepolizumab 100 mg SC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	177[17]	174[18]	184[19]	
Units: Scores on a scale				
least squares mean (standard error)	-9 (± 1.16)	-15.4 (± 1.16)	-16 (± 1.13)	

Notes:

[17] - ITT Population. Only participants with a Baseline and Week 32 assessment were included.

[18] - ITT Population. Only participants with a Baseline and Week 32 assessment were included.

[19] - ITT Population. Only participants with a Baseline and Week 32 assessment were included.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious AEs were defined as events occurring from the first dose of investigational product until 28 days after the last dose of investigational product.

Adverse event reporting additional description:

Serious adverse events (SAEs) and Non-serious AEs were collected in members of Intent-to-Treat (ITT) Population, comprised of all participants who were randomized and who received at least one dose of study medication. The number of occurrences for non-serious AEs was not collected; therefore, 0 has been entered.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo IV plus placebo SC every 4 weeks (for a total of 8 doses), with the last dose at Week 28. The SC dose and the IV dose were administered into separate arms. A topical anaesthetic was permitted at the injection site to minimize discomfort, as needed. Rescue personnel and rescue medications (salbutamol/albuterol) /equipment were available throughout the study.

Reporting group title	Mepolizumab 75 mg IV

Reporting group description:

Participants received mepolizumab 75 mg IV plus placebo SC every 4 weeks (for a total of 8 doses), with the last dose at Week 28. The SC dose and the IV dose were administered into separate arms. A topical anaesthetic was permitted at the injection site to minimize discomfort, as needed. Rescue personnel and rescue medications (salbutamol/albuterol) /equipment were available throughout the study.

Reporting group title	Mepolizumab 100 mg SC

Reporting group description:

Participants received placebo IV plus mepolizumab 100 mg SC every 4 weeks (for a total of 8 doses), with the last dose at Week 28. The SC dose and the IV dose were administered into separate arms. A topical anaesthetic was permitted at the injection site to minimize discomfort, as needed. Rescue personnel and rescue medications (salbutamol/albuterol) /equipment were available throughout the study.

Serious adverse events	Placebo	Mepolizumab 75 mg IV	Mepolizumab 100 mg SC
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 191 (14.14%)	14 / 191 (7.33%)	16 / 194 (8.25%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 191 (0.52%)	0 / 191 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Asthma			
subjects affected / exposed	14 / 191 (7.33%)	9 / 191 (4.71%)	5 / 194 (2.58%)
occurrences causally related to treatment / all	0 / 19	0 / 10	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 191 (0.00%)	0 / 194 (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
Psychiatric disorders			
Major depression			
subjects affected / exposed	1 / 191 (0.52%)	0 / 191 (0.00%)	0 / 194 (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			
Contusion			
subjects affected / exposed	1 / 191 (0.52%)	0 / 191 (0.00%)	0 / 194 (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
Fractured coccyx			
subjects affected / exposed	0 / 191 (0.00%)	1 / 191 (0.52%)	0 / 194 (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
Heat stroke			
subjects affected / exposed	1 / 191 (0.52%)	0 / 191 (0.00%)	0 / 194 (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
Inflammation of wound			
subjects affected / exposed	0 / 191 (0.00%)	0 / 191 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			

subjects affected / exposed	0 / 191 (0.00%)	1 / 191 (0.52%)	0 / 194 (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
Road traffic accident			
subjects affected / exposed	1 / 191 (0.52%)	0 / 191 (0.00%)	0 / 194 (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
Tendon rupture			
subjects affected / exposed	0 / 191 (0.00%)	1 / 191 (0.52%)	0 / 194 (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
Congenital, familial and genetic disorders			
Intracranial lipoma			
subjects affected / exposed	1 / 191 (0.52%)	0 / 191 (0.00%)	0 / 194 (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			
Atrial flutter			
subjects affected / exposed	0 / 191 (0.00%)	0 / 191 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 191 (0.52%)	0 / 191 (0.00%)	0 / 194 (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
Sciatica			
subjects affected / exposed	0 / 191 (0.00%)	1 / 191 (0.52%)	0 / 194 (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			
Gastrointestinal motility disorder			

subjects affected / exposed	0 / 191 (0.00%)	1 / 191 (0.52%)	0 / 194 (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
Large intestine perforation			
subjects affected / exposed	0 / 191 (0.00%)	0 / 191 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal spasm			
subjects affected / exposed	1 / 191 (0.52%)	0 / 191 (0.00%)	0 / 194 (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			
Gallbladder disorder			
subjects affected / exposed	0 / 191 (0.00%)	0 / 191 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 191 (0.00%)	1 / 191 (0.52%)	0 / 194 (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
Dyshidrotic eczema			
subjects affected / exposed	0 / 191 (0.00%)	0 / 191 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 191 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus ureteric			
subjects affected / exposed	1 / 191 (0.52%)	0 / 191 (0.00%)	0 / 194 (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

Calculus urethral			
subjects affected / exposed	1 / 191 (0.52%)	0 / 191 (0.00%)	0 / 194 (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
Nephrogenic diabetes insipidus			
subjects affected / exposed	0 / 191 (0.00%)	0 / 191 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	1 / 191 (0.52%)	0 / 191 (0.00%)	0 / 194 (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			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 191 (0.52%)	0 / 191 (0.00%)	0 / 194 (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 chest pain			
subjects affected / exposed	0 / 191 (0.00%)	0 / 191 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 191 (0.00%)	0 / 194 (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
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 191 (1.05%)	0 / 191 (0.00%)	0 / 194 (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
Herpes zoster			
subjects affected / exposed	0 / 191 (0.00%)	0 / 191 (0.00%)	2 / 194 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Clostridium difficile infection			
subjects affected / exposed	1 / 191 (0.52%)	0 / 191 (0.00%)	0 / 194 (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
Croup infectious			
subjects affected / exposed	0 / 191 (0.00%)	0 / 191 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 191 (0.00%)	0 / 191 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 191 (0.00%)	0 / 191 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 191 (0.00%)	0 / 191 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 191 (0.52%)	0 / 191 (0.00%)	0 / 194 (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	0 / 191 (0.00%)	0 / 191 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 191 (0.00%)	1 / 191 (0.52%)	0 / 194 (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
Vulval abscess			

subjects affected / exposed	1 / 191 (0.52%)	0 / 191 (0.00%)	0 / 194 (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

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

Non-serious adverse events	Placebo	Mepolizumab 75 mg IV	Mepolizumab 100 mg SC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	139 / 191 (72.77%)	141 / 191 (73.82%)	131 / 194 (67.53%)
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 191 (2.09%)	6 / 191 (3.14%)	3 / 194 (1.55%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	33 / 191 (17.28%)	46 / 191 (24.08%)	39 / 194 (20.10%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	8 / 191 (4.19%)	4 / 191 (2.09%)	6 / 194 (3.09%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	6 / 191 (3.14%)	1 / 191 (0.52%)	5 / 194 (2.58%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	6 / 191 (3.14%)	5 / 191 (2.62%)	17 / 194 (8.76%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	9 / 191 (4.71%)	8 / 191 (4.19%)	5 / 194 (2.58%)
occurrences (all)	0	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	3 / 191 (1.57%)	6 / 191 (3.14%)	2 / 194 (1.03%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	11 / 191 (5.76%)	4 / 191 (2.09%)	5 / 194 (2.58%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	4 / 191 (2.09%)	7 / 191 (3.66%)	7 / 194 (3.61%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	8 / 191 (4.19%)	4 / 191 (2.09%)	5 / 194 (2.58%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 191 (1.57%)	2 / 191 (1.05%)	7 / 194 (3.61%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	3 / 191 (1.57%)	0 / 191 (0.00%)	6 / 194 (3.09%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	16 / 191 (8.38%)	11 / 191 (5.76%)	9 / 194 (4.64%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	15 / 191 (7.85%)	12 / 191 (6.28%)	7 / 194 (3.61%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	9 / 191 (4.71%)	8 / 191 (4.19%)	5 / 194 (2.58%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	1 / 191 (0.52%)	5 / 191 (2.62%)	7 / 194 (3.61%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	4 / 191 (2.09%)	6 / 191 (3.14%)	2 / 194 (1.03%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	2 / 191 (1.05%)	2 / 191 (1.05%)	9 / 194 (4.64%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	7 / 191 (3.66%)	11 / 191 (5.76%)	14 / 194 (7.22%)
occurrences (all)	0	0	0
Arthralgia			
subjects affected / exposed	9 / 191 (4.71%)	10 / 191 (5.24%)	11 / 194 (5.67%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	10 / 191 (5.24%)	3 / 191 (1.57%)	8 / 194 (4.12%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	6 / 191 (3.14%)	3 / 191 (1.57%)	3 / 194 (1.55%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	46 / 191 (24.08%)	45 / 191 (23.56%)	33 / 194 (17.01%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	27 / 191 (14.14%)	22 / 191 (11.52%)	24 / 194 (12.37%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	18 / 191 (9.42%)	11 / 191 (5.76%)	18 / 194 (9.28%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	16 / 191 (8.38%)	14 / 191 (7.33%)	9 / 194 (4.64%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	6 / 191 (3.14%)	10 / 191 (5.24%)	5 / 194 (2.58%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	6 / 191 (3.14%)	10 / 191 (5.24%)	3 / 194 (1.55%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	2 / 191 (1.05%)	5 / 191 (2.62%)	8 / 194 (4.12%)
occurrences (all)	0	0	0
Pharyngitis			

subjects affected / exposed	3 / 191 (1.57%)	5 / 191 (2.62%)	6 / 194 (3.09%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	4 / 191 (2.09%)	7 / 191 (3.66%)	1 / 194 (0.52%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2012	Clarified 2 exclusion criteria

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported