Clinical trial results:
Study 117113: Mepolizumab vs. Placebo as add-on treatment for frequently exacerbating COPD patients characterized by eosinophil level

Summary

EudraCT number	2013-004297-98
Trial protocol	NL SK DE GB DK RO
Global end of trial date	16 January 2017

Results information

Result version number	v1
This version publication date	28 January 2018
First version publication date	28 January 2018

Trial information

Trial identification

Sponsor protocol code	117113

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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of mepolizumab 100 milligrams (mg) and 300 mg subcutaneous (SC) given every 4 weeks compared to placebo on the frequency of moderate and severe exacerbations in chronic obstructive pulmonary disease (COPD) participants at high risk of exacerbations despite the use of optimized standard of care background therapy.

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 April 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	Denmark: 23
Country: Number of subjects enrolled	Germany: 93
Country: Number of subjects enrolled	Netherlands: 52
Country: Number of subjects enrolled	United Kingdom: 22
Country: Number of subjects enrolled	Romania: 76
Country: Number of subjects enrolled	Slovakia: 30
Country: Number of subjects enrolled	Ukraine: 32
Country: Number of subjects enrolled	Japan: 40
Country: Number of subjects enrolled	Korea, Republic of: 70
Country: Number of subjects enrolled	Taiwan: 12
Country: Number of subjects enrolled	United States: 79
Country: Number of subjects enrolled	Argentina: 84
Country: Number of subjects enrolled	Chile: 34
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Canada: 17
Worldwide total number of subjects	675
EEA total number of subjects	296

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)	0
Adults (18-64 years)	316
From 65 to 84 years	356
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Participants with chronic obstructive pulmonary disease (COPD) with frequent exacerbations and on high dose inhaled corticosteroid (ICS)-based triple inhaled maintenance therapy were included in study. Participants were randomized to receive mepolizumab (100 or 300 milligrams [mg]) or placebo by subcutaneous (SC) injection every 4 weeks for 52 week

Pre-assignment

Screening details:

A total of 1071 participants were enrolled of which 59 were pre-screen failures; 337 were screen failures. 674 were randomized and received at least one dose of study treatment and included in the modified intent to treat (mITT) population. One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.

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, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Eligible participants were randomized to and received placebo by SC injection every 4 weeks for up to 52 weeks in addition to their standard of care (SoC) therapy. Salbutamol metered dose inhaler (MDI) was issued for use as rescue medication throughout the study.

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 was 0.9 percent sodium chloride solution, which was administered as three SC injections every 4 weeks up to 52 weeks along with standard of care therapy.

Arm title	Mepolizumab 100 mg SC

Arm description:

Eligible participants were randomized to and received mepolizumab 100 mg by SC injection every 4 weeks for up to 52 weeks in addition to their SoC therapy. Salbutamol MDI was issued for use as rescue medication throughout the study.

Arm type	Experimental
Investigational medicinal product name	Mepolizumab 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Mepolizumab was available as lyophilized cake which was reconstituted with Sterile water for injection prior to use. Mepolizumab 100 mg was administered as three SC injections given every 4 weeks for up to 52 weeks along with standard of care therapy.

Arm title	Mepolizumab 300 mg SC

Arm description:

Eligible participants were randomized to and received mepolizumab 300 mg by SC injection every 4 weeks for up to 52 weeks in addition to their SoC therapy. Salbutamol MDI was issued for use as rescue medication throughout the study.

Arm type	Experimental
Investigational medicinal product name	Mepolizumab 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Mepolizumab was available as lyophilized cake which was reconstituted with Sterile water for injection prior to use. Mepolizumab 300 mg was administered as three SC injections given every 4 weeks for up to 52 weeks along with standard of care therapy.

Number of subjects in period 1[1]	Placebo	Mepolizumab 100 mg SC	Mepolizumab 300 mg SC
Started	226	223	225
Completed Investigational Product (IP)	170 [2]	196 [3]	183 [4]
Not completed IP	56 [5]	27 [6]	42 [7]
Withdrew IP due to: Adverse event	27 [8]	9 [9]	25 [10]
Withdrew IP due to: stopping criteria	1 [11]	1 [12]	0 [13]
Withdrew IP due to: Lack of efficacy	6 [14]	2 [15]	2 [16]
Withdrew IP due to: Protocol deviation	2 [17]	0 [18]	1 [19]
Withdrew IP due to: Lost to Follow-up	1 [20]	1 [21]	1 [22]
Withdrew IP due to: Physician decision	2 [23]	3 [24]	1 [25]
Withdrew IP due to: Withdrawal by subj.	16 [26]	11 [27]	11 [28]
Withdrew IP due to: site closed	1 [29]	0 [30]	1 [31]
Completed	185	206	195
Not completed	41	17	30
Adverse event, serious fatal	7	4	8
Physician decision	3	3	2
Consent withdrawn by subject	15	7	11
Adverse event, non-fatal	11	3	5
Lost to follow-up	2	-	1
Lack of efficacy	3	-	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: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving

study treatment.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.

[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.

[10] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.

[11] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.

[12] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.

[13] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.

[14] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.

[15] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.

[16] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.
[17] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.
[18] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.
[19] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.
[20] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.
[21] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.
[22] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.
[23] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.
[24] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.
[25] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.
[26] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.
[27] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.
[28] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.
[29] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that

completed, minus those who left.

Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.

[30] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.

[31] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Eligible participants were randomized to and received placebo by SC injection every 4 weeks for up to 52 weeks in addition to their standard of care (SoC) therapy. Salbutamol metered dose inhaler (MDI) was issued for use as rescue medication throughout the study.	
Reporting group title	Mepolizumab 100 mg SC
Reporting group description:	
Eligible participants were randomized to and received mepolizumab 100 mg by SC injection every 4 weeks for up to 52 weeks in addition to their SoC therapy. Salbutamol MDI was issued for use as rescue medication throughout the study.	
Reporting group title	Mepolizumab 300 mg SC
Reporting group description:	
Eligible participants were randomized to and received mepolizumab 300 mg by SC injection every 4 weeks for up to 52 weeks in addition to their SoC therapy. Salbutamol MDI was issued for use as rescue medication throughout the study.	

Reporting group values	Placebo	Mepolizumab 100 mg SC	Mepolizumab 300 mg SC
Number of subjects	226	223	225
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	65.8	64.8	64.8
standard deviation	± 8.64	± 9.06	± 8.96
Gender categorical Units: Subjects			
Female	70	91	67
Male	156	132	158
Race/Ethnicity, Customized Units: Subjects			
Asian-Central/South Asian Heritage	0	0	1
Asian-East Asian Heritage	25	26	26
Asian-Japanese Heritage	14	13	13
Asian-South East Asian Heritage	3	2	1
Black or African American	2	4	2
White-White/Caucasian/European Heritage	182	178	182

Reporting group values	Total		
Number of subjects	674		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	228		
Male	446		
Race/Ethnicity, Customized Units: Subjects			
Asian-Central/South Asian Heritage	1		
Asian-East Asian Heritage	77		
Asian-Japanese Heritage	40		
Asian-South East Asian Heritage	6		
Black or African American	8		
White-White/Caucasian/European Heritage	542		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Eligible participants were randomized to and received placebo by SC injection every 4 weeks for up to 52 weeks in addition to their standard of care (SoC) therapy. Salbutamol metered dose inhaler (MDI) was issued for use as rescue medication throughout the study.	
Reporting group title	Mepolizumab 100 mg SC
Reporting group description:	
Eligible participants were randomized to and received mepolizumab 100 mg by SC injection every 4 weeks for up to 52 weeks in addition to their SoC therapy. Salbutamol MDI was issued for use as rescue medication throughout the study.	
Reporting group title	Mepolizumab 300 mg SC
Reporting group description:	
Eligible participants were randomized to and received mepolizumab 300 mg by SC injection every 4 weeks for up to 52 weeks in addition to their SoC therapy. Salbutamol MDI was issued for use as rescue medication throughout the study.	

Primary: Rate of moderate or severe exacerbations

End point title	Rate of moderate or severe exacerbations
End point description:	
Moderate exacerbations are defined as clinically significant exacerbations that require treatment with oral/systemic corticosteroids and/or antibiotics. Severe exacerbations are defined as clinically significant exacerbations that require in-patient hospitalization (>=24 hours) or result in death. Moderate and severe exacerbations occurring from the start of investigational product (IP) up to the Week 52 visit, including exacerbations reported after early discontinuation from IP by participants who remained in the study, were included in the analysis. The analysis was performed on the modified intent-to-treat (mITT) Population (all randomized participants who received at least one dose of study treatment).	
End point type	Primary
End point timeframe:	
From randomization to Week 52	

End point values	Placebo	Mepolizumab 100 mg SC	Mepolizumab 300 mg SC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	226[1]	223[2]	225[3]	
Units: Rate per year				
number (not applicable)				
Rate per year	1.49	1.19	1.27	

Notes:

[1] - mITT Population

[2] - mITT Population

[3] - mITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Analysis using a negative binomial model with covariates of treatment, geographic region, no. of	

moderate/severe exacerbations in previous year, Baseline percent predicted FEV1, smoking status and offset of log (time in on- and off- treatment period)

Comparison groups	Mepolizumab 100 mg SC v Placebo
Number of subjects included in analysis	449
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.068 [4]
Method	Negative binomial model
Parameter estimate	Rate ratio (Mepolizumab 100/Placebo)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.98

Notes:

[4] - Adjusted p-value; Family wise type I error controlled within each endpoint using a Hochberg testing procedure

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Analysis using a negative binomial model with covariates of treatment, geographic region, no. of moderate/severe exacerbations in previous year, Baseline percent predicted FEV1, smoking status and offset of log (time in on- and off- treatment period)

Comparison groups	Mepolizumab 100 mg SC v Placebo
Number of subjects included in analysis	449
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034 [5]
Method	Negative binomial model
Parameter estimate	Rate ratio (Mepolizumab 100/Placebo)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.98

Notes:

[5] - Unadjusted p-value

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Analysis using a negative binomial model with covariates of treatment, geographic region, no. of moderate/severe exacerbations in previous year, Baseline percent predicted FEV1, smoking status and offset of log (time in on- and off- treatment period)

Comparison groups	Mepolizumab 300 mg SC v Placebo
Number of subjects included in analysis	451
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14 [6]
Method	Negative binomial model
Parameter estimate	Rate ratio (Mepolizumab 300/Placebo)
Point estimate	0.86

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.05

Notes:

[6] - Adjusted p-value; Family wise type I error controlled within each endpoint using a Hochberg testing procedure

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Analysis using a negative binomial model with covariates of treatment, geographic region, no. of moderate/severe exacerbations in previous year, Baseline percent predicted FEV1, smoking status and offset of log (time in on- and off- treatment period)

Comparison groups	Mepolizumab 300 mg SC v Placebo
Number of subjects included in analysis	451
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14 [7]
Method	Negative binomial model
Parameter estimate	Rate ratio (Mepolizumab 300/Placebo)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.05

Notes:

[7] - Unadjusted p-value

Secondary: Time to first moderate/severe exacerbation

End point title	Time to first moderate/severe exacerbation

End point description:

Kaplan Meier estimates of the probability of a moderate or severe exacerbation are expressed as the percentage of participants with an exacerbation over time (by Week 8, 16, 24, 32, 40, 48, 52). Analysis of time to first moderate/severe exacerbation was performed on the mITT population and included exacerbations reported on-treatment and those reported after early discontinuation from IP by participants who remained in the study.

End point type	Secondary

End point timeframe:

From randomization to Week 52

End point values	Placebo	Mepolizumab 100 mg SC	Mepolizumab 300 mg SC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	226[8]	223[9]	225[10]	
Units: Percentage of participants				
number (confidence interval 95%)				
Week 8	22.6 (17.7 to 28.6)	22.9 (17.9 to 29.0)	18.3 (13.8 to 24.0)	

Week 16	40.7 (34.6 to 47.5)	36.0 (30.0 to 42.6)	29.0 (23.5 to 35.4)	
Week 24	51.1 (44.6 to 57.8)	42.4 (36.2 to 49.2)	36.7 (30.8 to 43.4)	
Week 32	58.3 (51.8 to 64.9)	46.1 (39.8 to 52.9)	44.9 (38.7 to 51.7)	
Week 40	62.3 (55.8 to 68.7)	50.8 (44.4 to 57.6)	51.8 (45.4 to 58.6)	
Week 48	64.2 (57.8 to 70.6)	55.5 (49.1 to 62.2)	58.3 (51.9 to 64.9)	
Week 52	66.7 (60.2 to 73.1)	57.9 (51.5 to 64.5)	58.8 (52.4 to 65.3)	

Notes:

[8] - mITT Population

[9] - mITT Population

[10] - mITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Analysis performed using a Cox Proportional Hazards Model with covariates of treatment, geographic region, number of moderate/severe exacerbations in previous year, Baseline percent predicted FEV1 and smoking status

Comparison groups	Mepolizumab 100 mg SC v Placebo
Number of subjects included in analysis	449
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14 [11]
Method	Cox Proportional Hazards Model
Parameter estimate	Hazard Ratio (Mepolizumab 100/Placebo)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.04

Notes:

[11] - Adjusted p-value; Family wise type I error controlled within each endpoint using a Hochberg testing procedure

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Analysis performed using a Cox Proportional Hazards Model with covariates of treatment, geographic region, number of moderate/severe exacerbations in previous year, Baseline percent predicted FEV1 and smoking status

Comparison groups	Mepolizumab 100 mg SC v Placebo
Number of subjects included in analysis	449
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.103 [12]
Method	Cox Proportional Hazards Model
Parameter estimate	Hazard Ratio (Mepolizumab 100/Placebo)
Point estimate	0.82

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.04

Notes:

[12] - Unadjusted p-value

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Analysis performed using a Cox Proportional Hazards Model with covariates of treatment, geographic region, number of moderate/severe exacerbations in previous year, Baseline percent predicted FEV1 and smoking status

Comparison groups	Mepolizumab 300 mg SC v Placebo
Number of subjects included in analysis	451
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14 [13]
Method	Cox Proportional Hazards Model
Parameter estimate	Hazard Ratio (Mepolizumab 300/Placebo)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	0.97

Notes:

[13] - Adjusted p-value; Family wise type I error controlled within each endpoint using a Hochberg testing procedure

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Analysis performed using a Cox Proportional Hazards Model with covariates of treatment, geographic region, number of moderate/severe exacerbations in previous year, Baseline percent predicted FEV1 and smoking status

Comparison groups	Mepolizumab 300 mg SC v Placebo
Number of subjects included in analysis	451
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03 [14]
Method	Cox Proportional Hazards Model
Parameter estimate	Hazard Ratio (Mepolizumab 300/Placebo)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	0.97

Notes:

[14] - Unadjusted p-value

Secondary: Rate of COPD exacerbations requiring emergency department (ED) visits

and/or hospitalizations	
End point title	Rate of COPD exacerbations requiring emergency department (ED) visits and/or hospitalizations

End point description:

COPD exacerbations requiring an ED visit and/or hospitalization occurring from the start of IP up to the Week 52 visit, including exacerbations reported after early discontinuation from IP by participants who remained in the study, were included in the analysis. This analysis was performed on the mITT population.

End point type	Secondary

End point timeframe:

From randomization to Week 52

End point values	Placebo	Mepolizumab 100 mg SC	Mepolizumab 300 mg SC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	226[15]	223[16]	225[17]	
Units: Rate per year				
number (not applicable)				
Rate per year	0.28	0.17	0.23	

Notes:

[15] - mITT Population

[16] - mITT Population

[17] - mITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Analysis using a negative binomial model with covariates of treatment, geographic region, no. of moderate/severe exacerbations in previous year, Baseline percent predicted FEV1, smoking status and offset of log (time in on- and off- treatment period)

Comparison groups	Placebo v Mepolizumab 100 mg SC
Number of subjects included in analysis	449
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14 [18]
Method	Negative binomial model
Parameter estimate	Rate ratio (Mepolizumab 100/Placebo)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.98

Notes:

[18] - Adjusted p-value; Family wise type I error controlled within each endpoint using a Hochberg testing procedure

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Analysis using a negative binomial model with covariates of treatment, geographic region, no. of moderate/severe exacerbations in previous year, Baseline percent predicted FEV1, smoking status and

offset of log (time in on- and off- treatment period)

Comparison groups	Placebo v Mepolizumab 100 mg SC
Number of subjects included in analysis	449
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042 [19]
Method	Negative binomial model
Parameter estimate	Rate ratio (Mepolizumab 100/Placebo)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.98

Notes:

[19] - Unadjusted p-value

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Analysis using a negative binomial model with covariates of treatment, geographic region, no. of moderate/severe exacerbations in previous year, Baseline percent predicted FEV1, smoking status and offset of log (time in on- and off- treatment period)

Comparison groups	Placebo v Mepolizumab 300 mg SC
Number of subjects included in analysis	451
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.447 [20]
Method	Negative binomial model
Parameter estimate	Rate ratio (Mepolizumab 300/Placebo)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.34

Notes:

[20] - Adjusted p-value; Family wise type I error controlled within each endpoint using a Hochberg testing procedure

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Analysis using a negative binomial model with covariates of treatment, geographic region, no. of moderate/severe exacerbations in previous year, Baseline percent predicted FEV1, smoking status and offset of log (time in on- and off- treatment period)

Comparison groups	Placebo v Mepolizumab 300 mg SC
Number of subjects included in analysis	451
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.447 [21]
Method	Negative binomial model
Parameter estimate	Rate ratio (Mepolizumab 300/Placebo)
Point estimate	0.83

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.34

Notes:

[21] - Unadjusted p-value

Secondary: Change from Baseline in mean total St. George's Respiratory Questionnaire (SGRQ) score

End point title	Change from Baseline in mean total St. George's Respiratory Questionnaire (SGRQ) score

End point description:

The SGRQ for COPD is a 40-item questionnaire derived from the original SGRQ , designed to measure health impairment by addressing the frequency of respiratory symptoms and current state of the participant. SGRQ Total Scores range from 0 to 100 with higher scores indicating worse health-related quality of life and reductions indicating improvement. The Baseline value will be the last measurement collected prior to the first dose of investigational product. Change from Baseline is calculated as the post-dose visit value minus the Baseline value. Participants with a Baseline and at least one post-Baseline assessment were included in the analysis. Mean change from Baseline in SGRQ score at Week 52 has been presented.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo	Mepolizumab 100 mg SC	Mepolizumab 300 mg SC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	218[22]	218[23]	219[24]	
Units: Total score on SGRQ scale				
least squares mean (standard error)				
Total score on SGRQ scale	-3.1 (± 0.98)	-5.0 (± 0.95)	-3.3 (± 0.96)	

Notes:

[22] - mITT Population

[23] - mITT Population

[24] - mITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Analysis performed using mixed model repeated measures with covariates of Baseline SGRQ total score, geographic region, smoking status, treatment and visit, plus interaction terms for visit by Baseline and visit by treatment group.

Comparison groups	Placebo v Mepolizumab 100 mg SC
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.447 [25]
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	Mean difference(Mepolizumab 100-Placebo)
Point estimate	-1.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	0.8

Notes:

[25] - Adjusted p-value; Family wise type I error controlled within each endpoint using a Hochberg testing procedure

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Analysis performed using mixed model repeated measures with covariates of Baseline SGRQ total score, geographic region, smoking status, treatment and visit, plus interaction terms for visit by Baseline and visit by treatment group.

Comparison groups	Placebo v Mepolizumab 100 mg SC
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18 [26]
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	Mean difference(Mepolizumab 100-Placebo)
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	0.8

Notes:

[26] - Unadjusted p-value

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Analysis performed using mixed model repeated measures with covariates of Baseline SGRQ total score, geographic region, smoking status, treatment and visit, plus interaction terms for visit by Baseline and visit by treatment group.

Comparison groups	Placebo v Mepolizumab 300 mg SC
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.926 [27]
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	Mean difference(Mepolizumab 300-Placebo)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	2.6

Notes:

[27] - Adjusted p-value; Family wise type I error controlled within each endpoint using a Hochberg testing procedure

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Analysis performed using mixed model repeated measures with covariates of Baseline SGRQ total score, geographic region, smoking status, treatment and visit, plus interaction terms for visit by Baseline and visit by treatment group.

Comparison groups	Placebo v Mepolizumab 300 mg SC
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.926 [28]
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	Mean difference(Mepolizumab 300-Placebo)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	2.6

Notes:

[28] - Unadjusted p-value

Secondary: Change from Baseline in Mean COPD assessment test (CAT) score

End point title	Change from Baseline in Mean COPD assessment test (CAT) score

End point description:

The CAT is an 8-item questionnaire developed for use in routine clinical practice to measure the health status of participants with COPD. Each question is assessed on a 6-point scale ranging from 0 (no impairment) to 5 (maximum impairment) with the CAT score ranging from 0-40. Higher scores indicate greater disease impact with reductions indicating improvement. The Baseline value will be the last measurement collected prior to the first dose of investigational product. Change from Baseline is calculated as the post-dose visit value minus the Baseline value. Participants with a Baseline and at least one post-Baseline assessment were included in the analysis. Mean change from Baseline in CAT score at Week 52 has been presented.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Placebo	Mepolizumab 100 mg SC	Mepolizumab 300 mg SC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	222[29]	216[30]	219[31]	
Units: Score on CAT scale				
least squares mean (standard error)				
Score on CAT scale	-0.4 (± 0.42)	-1.6 (± 0.42)	-0.8 (± 0.42)	

Notes:

[29] - mITT Population

[30] - mITT Population

[31] - mITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Analysis performed using mixed model repeated measures with covariates of Baseline CAT score, geographic region, smoking status, treatment and visit, plus interaction terms for visit by Baseline and visit by treatment group.

Comparison groups	Mepolizumab 100 mg SC v Placebo
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.926 [32]
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	Mean difference(Mepolizumab 100-Placebo)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	0

Notes:

[32] - Adjusted p-value; Family wise type I error controlled within each endpoint using a Hochberg testing procedure

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Analysis performed using mixed model repeated measures with covariates of Baseline CAT score, geographic region, smoking status, treatment and visit, plus interaction terms for visit by Baseline and visit by treatment group.

Comparison groups	Mepolizumab 100 mg SC v Placebo
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.055 [33]
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	Mean difference(Mepolizumab 100-Placebo)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	0

Notes:

[33] - Unadjusted p-value

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Analysis performed using mixed model repeated measures with covariates of Baseline CAT score, geographic region, smoking status, treatment and visit, plus interaction terms for visit by Baseline and visit by treatment group.

Comparison groups	Mepolizumab 300 mg SC v Placebo

Number of subjects included in analysis	441
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.926 [34]
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	Mean difference(Mepolizumab 300-Placebo)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	0.8

Notes:

[34] - Adjusted p-value; Family wise type I error controlled within each endpoint using a Hochberg testing procedure

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Analysis performed using mixed model repeated measures with covariates of Baseline CAT score, geographic region, smoking status, treatment and visit, plus interaction terms for visit by Baseline and visit by treatment group.

Comparison groups	Mepolizumab 300 mg SC v Placebo
Number of subjects included in analysis	441
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.547 [35]
Method	Mixed Model Repeated Measures Analysis
Parameter estimate	Mean difference(Mepolizumab 300-Placebo)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	0.8

Notes:

[35] - Unadjusted p-value

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) collected from the start of study participation until the end of follow up (up to Week 60). On-treatment non-serious adverse events (AEs) reported from start of study treatment until 4 weeks after last dose.

Adverse event reporting additional description:

AEs and SAEs were collected in Safety Population which comprised of all randomized participants who received at least one dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Eligible participants were randomized to and received placebo by SC injection every 4 weeks for up to 52 weeks in addition to their SoC therapy. Salbutamol MDI was issued for use as rescue medication throughout the study.

Reporting group title	Mepolizumab 100 mg SC

Reporting group description:

Eligible participants were randomized to and received mepolizumab 100 mg by SC injection every 4 weeks for up to 52 weeks in addition to their SoC therapy. Salbutamol MDI was issued for use as rescue medication throughout the study.

Reporting group title	Mepolizumab 300 mg SC

Reporting group description:

Eligible participants were randomized to and received mepolizumab 300 mg by SC injection every 4 weeks for up to 52 weeks in addition to their SoC therapy. Salbutamol MDI was issued for use as rescue medication throughout the study.

Serious adverse events	Placebo	Mepolizumab 100 mg SC	Mepolizumab 300 mg SC
Total subjects affected by serious adverse events			
subjects affected / exposed	68 / 226 (30.09%)	57 / 223 (25.56%)	60 / 225 (26.67%)
number of deaths (all causes)	9	4	8
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			

subjects affected / exposed	1 / 226 (0.44%)	1 / 223 (0.45%)	0 / 225 (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
Non-small cell lung cancer			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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
Benign lung neoplasm			
subjects affected / exposed	0 / 226 (0.00%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowen's disease			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Gastric cancer			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Lung adenocarcinoma			
subjects affected / exposed	0 / 226 (0.00%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Malignant melanoma			

subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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
Oropharyngeal cancer			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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
Rectal adenocarcinoma			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Aortic stenosis			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Essential hypertension			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Hypertension			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Hypertensive crisis			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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
Hypotension			

subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Orthostatic hypotension			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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			
Non-cardiac chest pain			
subjects affected / exposed	1 / 226 (0.44%)	1 / 223 (0.45%)	0 / 225 (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
Pyrexia			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 226 (0.00%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
General physical health deterioration			
subjects affected / exposed	0 / 226 (0.00%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular stent thrombosis			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 226 (0.44%)	1 / 223 (0.45%)	0 / 225 (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

Prostatic obstruction			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	37 / 226 (16.37%)	25 / 223 (11.21%)	32 / 225 (14.22%)
occurrences causally related to treatment / all	0 / 52	0 / 34	0 / 54
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Acute respiratory failure			
subjects affected / exposed	2 / 226 (0.88%)	3 / 223 (1.35%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 226 (0.44%)	1 / 223 (0.45%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Pulmonary embolism			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 226 (0.00%)	0 / 223 (0.00%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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 respiratory failure			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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

Hypercapnia			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Hypoxia			
subjects affected / exposed	0 / 226 (0.00%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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
Pleurisy			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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 aspiration			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Pneumothorax spontaneous			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Delirium			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Investigations			

Haematocrit increased			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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			
Rib fracture			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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 neck fracture			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Foot fracture			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Humerus fracture			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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
Injection related reaction			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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
Meniscus injury			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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

Post procedural haemorrhage			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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
Spinal compression fracture			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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 myocardial infarction			
subjects affected / exposed	3 / 226 (1.33%)	1 / 223 (0.45%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Atrial fibrillation			
subjects affected / exposed	3 / 226 (1.33%)	3 / 223 (1.35%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Coronary artery disease			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress cardiomyopathy			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 226 (0.00%)	0 / 223 (0.00%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			

subjects affected / exposed	0 / 226 (0.00%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Angina unstable			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Arrhythmia			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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 arrest			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Cor pulmonale			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Myocardial infarction			
subjects affected / exposed	0 / 226 (0.00%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Cerebral ischaemia			

subjects affected / exposed	0 / 226 (0.00%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Haemorrhagic stroke			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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
Peroneal nerve palsy			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Post herpetic neuralgia			
subjects affected / exposed	0 / 226 (0.00%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 226 (0.00%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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	1 / 226 (0.44%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular fibrosis			

subjects affected / exposed	0 / 226 (0.00%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 226 (0.00%)	3 / 223 (1.35%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Diverticulum intestinal			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Gastric haemorrhage			
subjects affected / exposed	0 / 226 (0.00%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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 haemorrhage			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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
Ileus			

subjects affected / exposed	0 / 226 (0.00%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 226 (0.00%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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	0 / 226 (0.00%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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 urinary			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Haematuria			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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 colic			

subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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 tubular necrosis			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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 retention			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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
Rhabdomyolysis			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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
Spinal osteoarthritis			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Spondyloarthropathy			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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

Infections and infestations			
Pneumonia			
subjects affected / exposed	18 / 226 (7.96%)	16 / 223 (7.17%)	15 / 225 (6.67%)
occurrences causally related to treatment / all	0 / 19	0 / 21	0 / 16
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	5 / 226 (2.21%)	1 / 223 (0.45%)	3 / 225 (1.33%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 226 (0.44%)	3 / 223 (1.35%)	0 / 225 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 226 (0.00%)	3 / 223 (1.35%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 226 (0.44%)	1 / 223 (0.45%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pseudomonal			
subjects affected / exposed	0 / 226 (0.00%)	0 / 223 (0.00%)	2 / 225 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Upper respiratory tract infection			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall abscess			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Appendicitis			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Atypical mycobacterial infection			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Clostridium difficile colitis			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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
Colonic abscess			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Cystitis			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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 infection			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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 abscess			

subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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
Orchitis			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Osteomyelitis			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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
Pneumonia bacterial			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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 haemophilus			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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
Pneumonia necrotising			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	0 / 225 (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
Pneumonia pneumococcal			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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 tuberculosis			
subjects affected / exposed	0 / 226 (0.00%)	0 / 223 (0.00%)	1 / 225 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			

subjects affected / exposed	0 / 226 (0.00%)	0 / 223 (0.00%)	1 / 225 (0.44%)
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 infection			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	0 / 225 (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

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

Non-serious adverse events	Placebo	Mepolizumab 100 mg SC	Mepolizumab 300 mg SC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	137 / 226 (60.62%)	147 / 223 (65.92%)	137 / 225 (60.89%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 226 (0.88%)	7 / 223 (3.14%)	3 / 225 (1.33%)
occurrences (all)	2	7	3
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 226 (1.33%)	8 / 223 (3.59%)	7 / 225 (3.11%)
occurrences (all)	3	9	7
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 226 (8.85%)	34 / 223 (15.25%)	22 / 225 (9.78%)
occurrences (all)	29	62	39
General disorders and administration site conditions			

Injection site reaction			
subjects affected / exposed	10 / 226 (4.42%)	6 / 223 (2.69%)	11 / 225 (4.89%)
occurrences (all)	17	6	27
Pyrexia			
subjects affected / exposed	9 / 226 (3.98%)	6 / 223 (2.69%)	12 / 225 (5.33%)
occurrences (all)	9	7	17
Non-cardiac chest pain			
subjects affected / exposed	7 / 226 (3.10%)	5 / 223 (2.24%)	7 / 225 (3.11%)
occurrences (all)	7	8	8
Fatigue			
subjects affected / exposed	4 / 226 (1.77%)	6 / 223 (2.69%)	8 / 225 (3.56%)
occurrences (all)	4	6	8
Oedema peripheral			
subjects affected / exposed	3 / 226 (1.33%)	7 / 223 (3.14%)	4 / 225 (1.78%)
occurrences (all)	3	7	6
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	14 / 226 (6.19%)	13 / 223 (5.83%)	8 / 225 (3.56%)
occurrences (all)	14	16	12
Constipation			
subjects affected / exposed	10 / 226 (4.42%)	7 / 223 (3.14%)	5 / 225 (2.22%)
occurrences (all)	10	8	6
Nausea			
subjects affected / exposed	3 / 226 (1.33%)	9 / 223 (4.04%)	9 / 225 (4.00%)
occurrences (all)	3	10	13
Abdominal pain upper			
subjects affected / exposed	1 / 226 (0.44%)	9 / 223 (4.04%)	5 / 225 (2.22%)
occurrences (all)	1	9	5
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 226 (5.31%)	14 / 223 (6.28%)	16 / 225 (7.11%)
occurrences (all)	16	14	22
Dyspnoea			
subjects affected / exposed	18 / 226 (7.96%)	12 / 223 (5.38%)	10 / 225 (4.44%)
occurrences (all)	19	14	17
Oropharyngeal pain			

subjects affected / exposed	4 / 226 (1.77%)	15 / 223 (6.73%)	11 / 225 (4.89%)
occurrences (all)	4	15	13
Chronic obstructive pulmonary disease			
subjects affected / exposed	5 / 226 (2.21%)	8 / 223 (3.59%)	10 / 225 (4.44%)
occurrences (all)	9	12	24
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	11 / 226 (4.87%)	15 / 223 (6.73%)	17 / 225 (7.56%)
occurrences (all)	11	18	21
Arthralgia			
subjects affected / exposed	6 / 226 (2.65%)	10 / 223 (4.48%)	6 / 225 (2.67%)
occurrences (all)	7	10	6
Pain in extremity			
subjects affected / exposed	5 / 226 (2.21%)	7 / 223 (3.14%)	6 / 225 (2.67%)
occurrences (all)	6	7	10
Musculoskeletal pain			
subjects affected / exposed	2 / 226 (0.88%)	4 / 223 (1.79%)	7 / 225 (3.11%)
occurrences (all)	2	4	8
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	48 / 226 (21.24%)	39 / 223 (17.49%)	40 / 225 (17.78%)
occurrences (all)	65	57	52
Upper respiratory tract infection			
subjects affected / exposed	20 / 226 (8.85%)	16 / 223 (7.17%)	12 / 225 (5.33%)
occurrences (all)	27	19	15
Pneumonia			
subjects affected / exposed	8 / 226 (3.54%)	10 / 223 (4.48%)	10 / 225 (4.44%)
occurrences (all)	9	13	11
Bronchitis			
subjects affected / exposed	8 / 226 (3.54%)	8 / 223 (3.59%)	11 / 225 (4.89%)
occurrences (all)	8	12	15
Sinusitis			
subjects affected / exposed	7 / 226 (3.10%)	8 / 223 (3.59%)	7 / 225 (3.11%)
occurrences (all)	11	11	9
Influenza			

subjects affected / exposed	11 / 226 (4.87%)	6 / 223 (2.69%)	3 / 225 (1.33%)
occurrences (all)	11	7	3
Oral candidiasis			
subjects affected / exposed	5 / 226 (2.21%)	3 / 223 (1.35%)	8 / 225 (3.56%)
occurrences (all)	7	3	9
Rhinitis			
subjects affected / exposed	5 / 226 (2.21%)	7 / 223 (3.14%)	4 / 225 (1.78%)
occurrences (all)	6	9	4
Urinary tract infection			
subjects affected / exposed	7 / 226 (3.10%)	7 / 223 (3.14%)	1 / 225 (0.44%)
occurrences (all)	8	8	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2014	Amendment No. 1 - Removal of 36-Item Short Form Survey (SF-36) health outcomes endpoint - Removal of electrocardiogram (ECG) at Visit 2 - Update of ECG exclusion and discontinuation criteria - Addition of adverse event causality assessment guidance language - Update of chest x-ray randomization criterion for Germany - Wording edited for consistency and clarification of statements in multiple sections

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported