



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

Justification: One participant randomized to mepolizumab 300 mg was withdrawn without receiving study treatment.

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 occurrences causally related to treatment / all deaths causally related to treatment / all | 18 / 226 (7.96%) 0 / 19 0 / 2 | 16 / 223 (7.17%) 0 / 21 0 / 0 | 15 / 225 (6.67%) 0 / 16 0 / 1 |
| Infective exacerbation of chronic obstructive airways disease subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 5 / 226 (2.21%) 0 / 6 0 / 0 | 1 / 223 (0.45%) 0 / 1 0 / 0 | 3 / 225 (1.33%) 0 / 4 0 / 0 |
| Sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 226 (0.44%) 0 / 1 0 / 0 | 3 / 223 (1.35%) 0 / 3 0 / 1 | 0 / 225 (0.00%) 0 / 0 0 / 0 |
| Urinary tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 226 (0.00%) 0 / 0 0 / 0 | 3 / 223 (1.35%) 0 / 3 0 / 0 | 1 / 225 (0.44%) 0 / 1 0 / 0 |
| Lower respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 226 (0.44%) 0 / 1 0 / 0 | 1 / 223 (0.45%) 0 / 1 0 / 0 | 1 / 225 (0.44%) 0 / 1 0 / 0 |
| Bronchitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 226 (0.44%) 0 / 1 0 / 0 | 0 / 223 (0.00%) 0 / 0 0 / 0 | 1 / 225 (0.44%) 0 / 1 0 / 0 |
| Influenza subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 226 (0.44%) 0 / 1 0 / 0 | 0 / 223 (0.00%) 0 / 0 0 / 0 | 1 / 225 (0.44%) 0 / 1 0 / 0 |
| Pneumonia pseudomonal subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 226 (0.00%) 0 / 0 0 / 0 | 0 / 223 (0.00%) 0 / 0 0 / 0 | 2 / 225 (0.89%) 0 / 3 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 occurrences (all) | 10 / 226 (4.42%) 17 | 6 / 223 (2.69%) 6 | 11 / 225 (4.89%) 27 |
| Pyrexia subjects affected / exposed occurrences (all) | 9 / 226 (3.98%) 9 | 6 / 223 (2.69%) 7 | 12 / 225 (5.33%) 17 |
| Non-cardiac chest pain subjects affected / exposed occurrences (all) | 7 / 226 (3.10%) 7 | 5 / 223 (2.24%) 8 | 7 / 225 (3.11%) 8 |
| Fatigue subjects affected / exposed occurrences (all) | 4 / 226 (1.77%) 4 | 6 / 223 (2.69%) 6 | 8 / 225 (3.56%) 8 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 3 / 226 (1.33%) 3 | 7 / 223 (3.14%) 7 | 4 / 225 (1.78%) 6 |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 14 / 226 (6.19%) 14 | 13 / 223 (5.83%) 16 | 8 / 225 (3.56%) 12 |
| Constipation subjects affected / exposed occurrences (all) | 10 / 226 (4.42%) 10 | 7 / 223 (3.14%) 8 | 5 / 225 (2.22%) 6 |
| Nausea subjects affected / exposed occurrences (all) | 3 / 226 (1.33%) 3 | 9 / 223 (4.04%) 10 | 9 / 225 (4.00%) 13 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 226 (0.44%) 1 | 9 / 223 (4.04%) 9 | 5 / 225 (2.22%) 5 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 12 / 226 (5.31%) 16 | 14 / 223 (6.28%) 14 | 16 / 225 (7.11%) 22 |
| Dyspnoea subjects affected / exposed occurrences (all) | 18 / 226 (7.96%) 19 | 12 / 223 (5.38%) 14 | 10 / 225 (4.44%) 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 <ul style="list-style-type: none">- 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