# Clinical trial results:
# A Phase III, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Lebrikizumab in Patients with Uncontrolled Asthma who are on Inhaled Corticosteroids and a Second Controller Medication

## Summary

| | |
|---|---|
| EudraCT number | 2013-000176-15 |
| Trial protocol | DE BE GB HU IT CZ ES PL BG SK |
| Global end of trial date | 03 January 2017 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 03 January 2018 |
| First version publication date | 03 January 2018 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | GB28689 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01868061 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 03 January 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 03 January 2017 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

Primary purpose of this study is to determine the efficacy and safety of lebrikizumab in subjects with asthma whose disease remains uncontrolled despite daily treatment with inhaled corticosteroid (ICS) therapy and at least one second controller medication. Subjects were randomised in 1:1:1 ratio to receive double-blind treatment with either lebrikizumab ("high" or "low") or placebo, administered as subcutaneous (SC) injection every 4 weeks for 52 weeks, in addition to their standard-of-care therapy. This was followed by a 52-week double-blind active treatment extension. Subjects who were assigned to placebo during the placebo-controlled period of the trial were re-randomised at Week 52 to receive blinded SC lebrikizumab 37.5 milligrams (mg) or 125 mg every 4 weeks from Week 52 to Week 104. Time on study treatment up to 104 weeks. After study treatment, subjects completed a 20-week safety follow-up.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy:

a) Inhaled corticosteroids (ICS) therapy at a total daily dose of 500 − 2000 microgram (mcg) of fluticasone propionate dry powder inhaler (DPI) or equivalent for ≥ 6 months prior to Visit 1, with no changes within 4 weeks prior to Visit 1 and no anticipated changes throughout the study. b) Second controller medication (Long-acting β adrenoceptor agonists (LABA), Leukotriene Receptor Antagonists (LTRA), Long-acting muscarinic antagonists (LAMA), or theophylline) for 6 months prior to Visit 1, with no changes within 4 weeks prior to Visit 1 and no anticipated changes throughout the study (except for theophylline dose, which may be adjusted on the basis of theophylline levels).

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 29 July 2013 |
| 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 | Japan: 56 |
| Country: Number of subjects enrolled | Korea, Republic of: 30 |
| Country: Number of subjects enrolled | Bulgaria: 82 |
| Country: Number of subjects enrolled | Czech Republic: 14 |
| Country: Number of subjects enrolled | Hungary: 11 |
| Country: Number of subjects enrolled | Poland: 140 |
| Country: Number of subjects enrolled | Romania: 19 |
| Country: Number of subjects enrolled | Russian Federation: 64 |
| Country: Number of subjects enrolled | Serbia: 10 |
| Country: Number of subjects enrolled | Slovakia: 14 |

| | |
|---|---|
| Country: Number of subjects enrolled | Ukraine: 95 |
| Country: Number of subjects enrolled | Argentina: 21 |
| Country: Number of subjects enrolled | Mexico: 20 |
| Country: Number of subjects enrolled | Peru: 42 |
| Country: Number of subjects enrolled | Canada: 20 |
| Country: Number of subjects enrolled | United States: 297 |
| Country: Number of subjects enrolled | Australia: 7 |
| Country: Number of subjects enrolled | Belgium: 13 |
| Country: Number of subjects enrolled | Spain: 21 |
| Country: Number of subjects enrolled | France: 8 |
| Country: Number of subjects enrolled | United Kingdom: 3 |
| Country: Number of subjects enrolled | Israel: 32 |
| Country: Number of subjects enrolled | Italy: 7 |
| Country: Number of subjects enrolled | New Zealand: 8 |
| Country: Number of subjects enrolled | South Africa: 33 |
| Worldwide total number of subjects | 1067 |
| EEA total number of subjects | 332 |

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) | 909 |
| From 65 to 84 years | 158 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Subjects with asthma, whose disease remained uncontrolled despite daily treatment with inhaled corticosteroid (ICS) therapy and at least one second controller medication, were recruited in 26 countries.

### Pre-assignment

Screening details:

Subject randomisation was stratified by baseline serum periostin level, history of asthma exacerbations within the last 12 months, baseline asthma medications and country.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo |

Arm description:

Subjects received SC injection of lebrikizumab matching placebo every 4 weeks for 52 weeks during the placebo-controlled period. Subjects then completed a 20-week safety follow-up.

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

Dosage and administration details:

Subjects received lebrikizumab matching placebo by SC injection every 4 weeks.

| | |
|---|---|
| **Arm title** | Placebo/Lebrikizumab (37.5 mg) |

Arm description:

Subjects received SC injection of lebrikizumab matching placebo every 4 weeks for 52 weeks during the placebo-controlled period followed by SC injection of lebrikizumab at 37.5 mg for another 52 weeks during the active treatment extension period. After study treatment, subjects completed a 20-week safety follow-up.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Lebrikizumab |
| Investigational medicinal product code | RO5490255 |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received 37.5 mg lebrikizumab by SC injection every 4 weeks.

| | |
|---|---|
| **Arm title** | Placebo/Lebrikizumab (125 mg) |

Arm description:

Subjects received SC injection of lebrikizumab matching placebo every 4 weeks for 52 weeks during the placebo-controlled period followed by SC injection of lebrikizumab at 125 mg for another 52 weeks during active treatment extension period. After study treatment, subjects completed a 20-week safety follow-up.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Lebrikizumab |
| Investigational medicinal product code | RO5490255 |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received 125 mg lebrikizumab by SC injection every 4 weeks.

| | |
|---|---|
| **Arm title** | Lebrikizumab (37.5 mg) |

Arm description:

Subjects received SC injection of lebrikizumab (37.5 mg) every 4 weeks for 104 weeks. After study treatment, subjects completed a 20-week safety follow-up.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Lebrikizumab |
| Investigational medicinal product code | RO5490255 |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received 37.5 mg lebrikizumab by SC injection every 4 weeks.

| | |
|---|---|
| **Arm title** | Lebrikizumab (125 mg) |

Arm description:

Subjects received SC injection of lebrikizumab (125 mg) every 4 weeks for 104 weeks. After study treatment, subjects completed a 20-week safety follow-up.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Lebrikizumab |
| Investigational medicinal product code | RO5490255 |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received 125 mg lebrikizumab by SC injection every 4 weeks.

| **Number of subjects in period 1** | Placebo | Placebo/Lebrikizumab (37.5 mg) | Placebo/Lebrikizumab (125 mg) |
|---|---|---|---|
| Started | 44 | 156 | 154 |
| Completed | 14 | 139 | 140 |
| Not completed | 30 | 17 | 14 |
| Non-Compliance | 2 | - | - |
| Physician decision | 1 | - | - |
| Withdrawal By Subject | 18 | 10 | 8 |
| Adverse Event | 3 | 1 | 4 |
| Death | - | - | - |
| Pregnancy | - | - | - |
| Lost to follow-up | 2 | 5 | 2 |
| Reason not specified | 3 | - | - |

| | | | |
|---|---|---|---|
| Lack of efficacy | 1 | 1 | - |

| **Number of subjects in period 1** | Lebrikizumab (37.5 mg) | Lebrikizumab (125 mg) |
|---|---|---|
| Started | 356 | 357 |
| Completed | 291 | 292 |
| Not completed | 65 | 65 |
| Non-Compliance | - | 2 |
| Physician decision | 2 | 1 |
| Withdrawal By Subject | 51 | 42 |
| Adverse Event | 1 | 8 |
| Death | 1 | - |
| Pregnancy | 1 | - |
| Lost to follow-up | 6 | 6 |
| Reason not specified | 3 | 4 |
| Lack of efficacy | - | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Overall Period |

Reporting group description: -

| Reporting group values | Overall Period | Total | |
|---|---|---|---|
| Number of subjects | 1067 | 1067 | |
| Age Categorical<br>Units: Subjects | | | |
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | <br><br>50.2<br>± 13.0 | <br><br><br>- | |
| Gender Categorical<br>Units: Subjects | | | |
| Female | 658 | 658 | |
| Male | 409 | 409 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects received SC injection of lebrikizumab matching placebo every 4 weeks for 52 weeks during the placebo-controlled period. Subjects then completed a 20-week safety follow-up. | |
| Reporting group title | Placebo/Lebrikizumab (37.5 mg) |
| Reporting group description: | |
| Subjects received SC injection of lebrikizumab matching placebo every 4 weeks for 52 weeks during the placebo-controlled period followed by SC injection of lebrikizumab at 37.5 mg for another 52 weeks during the active treatment extension period. After study treatment, subjects completed a 20-week safety follow-up. | |
| Reporting group title | Placebo/Lebrikizumab (125 mg) |
| Reporting group description: | |
| Subjects received SC injection of lebrikizumab matching placebo every 4 weeks for 52 weeks during the placebo-controlled period followed by SC injection of lebrikizumab at 125 mg for another 52 weeks during active treatment extension period. After study treatment, subjects completed a 20-week safety follow-up. | |
| Reporting group title | Lebrikizumab (37.5 mg) |
| Reporting group description: | |
| Subjects received SC injection of lebrikizumab (37.5 mg) every 4 weeks for 104 weeks. After study treatment, subjects completed a 20-week safety follow-up. | |
| Reporting group title | Lebrikizumab (125 mg) |
| Reporting group description: | |
| Subjects received SC injection of lebrikizumab (125 mg) every 4 weeks for 104 weeks. After study treatment, subjects completed a 20-week safety follow-up. | |
| Subject analysis set title | Biomarker-High, Placebo |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Subjects in the biomarker high arms had Periostin levels >/= 50 nanograms per millilitre (ng/mL) and Eosinophil counts >/= 300 cells per microlitre (cells/mcL). Subjects in this arm received SC injection of lebrikizumab matching placebo every 4 weeks for 52 weeks during the placebo-controlled period (Period 1). | |
| Subject analysis set title | Biomarker-High, Lebrikizumab 37.5 mg |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Subjects in the biomarker high arms had Periostin levels >/= 50 ng/mL or Eosinophil counts >/= 300 cells/mcL. Subjects in this arm received SC injection of lebrikizumab (37.5 mg) every 4 weeks for 52 weeks during the placebo-controlled period (Period 1). | |
| Subject analysis set title | Biomarker-High, Lebrikizumab 125 mg |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Subjects in the biomarker high arms had Periostin levels >/= 50 ng/mL or Eosinophil counts >/= 300 cells/mcL. Subjects in this arm received SC injection of lebrikizumab (125 mg) every 4 weeks for 52 weeks during the placebo-controlled period (Period 1). | |
| Subject analysis set title | Biomarker-Low, Placebo |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Subjects in the biomarker low arms had Periostin levels < 50 ng/mL and Eosinophils < 300 cells/mcL. Subjects in this arm received SC injection of lebrikizumab matching placebo every 4 weeks for 52 weeks during the placebo-controlled period (Period 1). | |
| Subject analysis set title | Biomarker-Low, Lebrikizumab 37.5 mg |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Subjects in the biomarker low arms had Periostin levels < 50 ng/mL and Eosinophils < 300 cells/mcL. | |

Subjects in this arm received SC injection of lebrikizumab (37.5 mg) every 4 weeks for 52 weeks during the placebo-controlled period (Period 1).

| | |
|---|---|
| Subject analysis set title | Biomarker-Low, Lebrikizumab 125 mg |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Subjects in the biomarker low arms had Periostin levels < 50 ng/mL and Eosinophils < 300 cells/mcL. Subjects in this arm received SC injection of lebrikizumab (125 mg) every 4 weeks for 52 weeks during the placebo-controlled period (Period 1).

## Primary: Rate of Asthma Exacerbations During the 52-Week Placebo-Controlled Period

| | |
|---|---|
| End point title | Rate of Asthma Exacerbations During the 52-Week Placebo-Controlled Period |

End point description:

An asthma exacerbation is defined as new or increased asthma symptoms (including wheeze, cough, dyspnea, chest tightness, and/or night-time awakening due to these symptoms) that lead to treatment with systemic corticosteroids or to hospitalisation. Treatment with systemic corticosteroids is defined as treatment with oral, intravenous (IV), or intramuscular (IM) corticosteroids for at least 3 days or an emergency department visit with at least one dose of IV or IM corticosteroids. Reported is the rate of asthma exacerbations during the 52-week placebo-controlled period. ITT population included all subjects randomised in the study.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

Baseline up to 52 weeks

| End point values | Biomarker-High, Placebo | Biomarker-High, Lebrikizumab 37.5 mg | Biomarker-High, Lebrikizumab 125 mg | Biomarker-Low, Placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 247 | 257 | 251 | 107 |
| Units: Exacerbation rate | | | | |
| number (not applicable) | 0.73 | 0.54 | 0.54 | 0.34 |

| End point values | Biomarker-Low, Lebrikizumab 37.5 mg | Biomarker-Low, Lebrikizumab 125 mg | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 99 | 106 | | |
| Units: Exacerbation rate | | | | |
| number (not applicable) | 0.50 | 0.35 | | |

## Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | High: Lebrikizumab 125 mg vs Placebo |

Statistical analysis description:

Adjusted exacerbation rates and rate ratios are estimates from a Poisson regression model with over-dispersion adjusted for the following covariates in addition to log(patient years) as an offset: number of

asthma exacerbations within the last 12 months, baseline asthma medications, geographic region and a 3-level categorical variable (periostin high and eosinophil high, periostin high and eosinophil low, periostin low and eosinophil high).

| | |
|---|---|
| Comparison groups | Biomarker-High, Placebo v Biomarker-High, Lebrikizumab 125 mg |
| Number of subjects included in analysis | 498 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0571 |
| Method | Poisson regression |
| Parameter estimate | Rate Ratio |
| Point estimate | 0.74 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 1.01 |

| **Statistical analysis title** | High: Lebrikizumab 37.5 mg vs Placebo |
|---|---|

Statistical analysis description:

Adjusted exacerbation rates and rate ratios are estimates from a Poisson regression model with over-dispersion adjusted for the following covariates in addition to log(patient years) as an offset: number of asthma exacerbations within the last 12 months, baseline asthma medications, geographic region and a 3-level categorical variable (periostin high and eosinophil high, periostin high and eosinophil low, periostin low and eosinophil high).

| | |
|---|---|
| Comparison groups | Biomarker-High, Placebo v Biomarker-High, Lebrikizumab 37.5 mg |
| Number of subjects included in analysis | 504 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.056 |
| Method | Poisson regression |
| Parameter estimate | Rate Ratio |
| Point estimate | 0.74 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 1.01 |

| **Statistical analysis title** | Low: Lebrikizumab 125 mg vs Placebo |
|---|---|

Statistical analysis description:

Adjusted exacerbation rates and rate ratios are estimates from a Poisson regression model with over-dispersion adjusted for the following covariates in addition to log(patient years) as an offset: number of asthma exacerbations within the last 12 months, baseline asthma medications and geographic region.

| | |
|---|---|
| Comparison groups | Biomarker-Low, Placebo v Biomarker-Low, Lebrikizumab 125 mg |

| | |
|---|---|
| Number of subjects included in analysis | 213 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9099 |
| Method | Poisson regression |
| Parameter estimate | Rate Ratio |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 1.78 |

| **Statistical analysis title** | Low: Lebrikizumab 37.5 mg vs Placebo |
|---|---|

Statistical analysis description:

Adjusted exacerbation rates and rate ratios are estimates from a Poisson regression model with over-dispersion adjusted for the following covariates in addition to log(patient years) as an offset: number of asthma exacerbations within the last 12 months, baseline asthma medications and geographic region.

| | |
|---|---|
| Comparison groups | Biomarker-Low, Placebo v Biomarker-Low, Lebrikizumab 37.5 mg |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1462 |
| Method | Poisson regression |
| Parameter estimate | Rate Ratio |
| Point estimate | 1.47 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.88 |
| upper limit | 2.45 |

## Secondary: Absolute Change From Baseline in Pre-Bronchodilator Forced Expiratory Volume in 1 Second (FEV1 ) at Week 52

| End point title | Absolute Change From Baseline in Pre-Bronchodilator Forced Expiratory Volume in 1 Second (FEV1 ) at Week 52 |
|---|---|

End point description:

FEV1 is the maximal amount of air, which can be forcefully exhaled in one second. Measurements were performed before use of bronchodilator. Reported is the absolute change from baseline in FEV1 to the end of the placebo-controlled period at Week 52. ITT population included all subjects randomised in the study.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 52

| End point values | Biomarker-High, Placebo | Biomarker-High, Lebrikizumab 37.5 mg | Biomarker-High, Lebrikizumab 125 mg | Biomarker-Low, Placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 226 | 241 | 231 | 94 |
| Units: millilitre (mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=247,257,251,107,99,106) | 1839 (± 573) | 1809 (± 515) | 1836 (± 599) | 1995 (± 577) |
| Change at Week 52 (n=226,241,231,94,88,96) | 91 (± 383) | 184 (± 387) | 183 (± 424) | 85 (± 422) |

| End point values | Biomarker-Low, Lebrikizumab 37.5 mg | Biomarker-Low, Lebrikizumab 125 mg | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 88 | 96 | | |
| Units: millilitre (mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=247,257,251,107,99,106) | 1954 (± 593) | 1862 (± 537) | | |
| Change at Week 52 (n=226,241,231,94,88,96) | 98 (± 435) | 103 (± 383) | | |

## Statistical analyses

| Statistical analysis title | High: Lebrikizumab 125 mg vs Placebo |
|---|---|

Statistical analysis description:

Estimates are based on a MMRM analysis with an unstructured covariance matrix. Model used absolute change from baseline in pre-bronchodilator FEV1 as response variable and included terms for treatment, visit, treatment visit, baseline FEV1, baseline FEV1 visit, number of asthma exacerbations within last 12 months, baseline asthma medications, geographic region and a 3-level categorical variable (periostin high, eosinophil high, periostin high, eosinophil low, periostin low, eosinophil high).

| | |
|---|---|
| Comparison groups | Biomarker-High, Placebo v Biomarker-High, Lebrikizumab 125 mg |
| Number of subjects included in analysis | 457 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0216 |
| Method | Mixed Model Repeated Measures (MMRM) |
| Parameter estimate | Difference in Adjusted Means |
| Point estimate | 82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 12 |
| upper limit | 152 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 36 |

| **Statistical analysis title** | High: Lebrikizumab 37.5 mg vs Placebo |
|---|---|

Statistical analysis description:

Estimates are based on a MMRM analysis with an unstructured covariance matrix. Model used absolute change from baseline in pre-bronchodilator FEV1 as response variable and included terms for treatment, visit, treatment visit, baseline FEV1, baseline FEV1 visit, number of asthma exacerbations within last 12 months, baseline asthma medications, geographic region and a 3-level categorical variable (periostin high, eosinophil high, periostin high, eosinophil low, periostin low, eosinophil high).

| | |
|---|---|
| Comparison groups | Biomarker-High, Placebo v Biomarker-High, Lebrikizumab 37.5 mg |
| Number of subjects included in analysis | 467 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0143 |
| Method | Mixed Model Repeated Measures (MMRM) |
| Parameter estimate | Difference in Adjusted Means |
| Point estimate | 87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 18 |
| upper limit | 157 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 36 |

| **Statistical analysis title** | Low: Lebrikizumab 125 mg vs Placebo |
|---|---|

Statistical analysis description:

Estimates are based on a MMRM analysis with an unstructured covariance matrix. Model used absolute change from baseline in pre-bronchodilator FEV1 as response variable and included terms for treatment, visit, treatment visit, baseline FEV1, baseline FEV1 visit, number of asthma exacerbations within last 12 months, baseline asthma medications and geographic region.

| | |
|---|---|
| Comparison groups | Biomarker-Low, Placebo v Biomarker-Low, Lebrikizumab 125 mg |
| Number of subjects included in analysis | 190 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7456 |
| Method | Mixed Model Repeated Measures (MMRM) |
| Parameter estimate | Difference in Adjusted Means |
| Point estimate | 19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -97 |
| upper limit | 135 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 59 |

| **Statistical analysis title** | Low: Lebrikizumab 37.5 mg vs Placebo |
|---|---|

Statistical analysis description:

Estimates are based on a MMRM analysis with an unstructured covariance matrix. Model used absolute change from baseline in pre-bronchodilator FEV1 as response variable and included terms for treatment, visit, treatment visit, baseline FEV1, baseline FEV1 visit, number of asthma exacerbations within last 12 months, baseline asthma medications and geographic region.

| | |
|---|---|
| Comparison groups | Biomarker-Low, Placebo v Biomarker-Low, Lebrikizumab 37.5 mg |
| Number of subjects included in analysis | 182 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9907 |
| Method | Mixed Model Repeated Measures (MMRM) |
| Parameter estimate | Difference in Adjusted Means |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -117 |
| upper limit | 118 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 60 |

## Secondary: Time to First Asthma Exacerbation During the Placebo-Controlled Period

| End point title | Time to First Asthma Exacerbation During the Placebo-Controlled Period |
|---|---|

End point description:

An asthma exacerbation is defined as new or increased asthma symptoms (including wheeze, cough, dyspnea, chest tightness, and/or night-time awakening due to these symptoms) that lead to treatment with systemic corticosteroids or to hospitalisation. Treatment with systemic corticosteroids is defined as treatment with oral, intravenous (IV), or intramuscular (IM) corticosteroids for at least 3 days or an emergency department visit with at least one dose of IV or IM corticosteroids. Reported is the time to first asthma exacerbation during the 52-week placebo-controlled period. ITT population included all subjects randomised in the study. 9999 = not estimable

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline up to 52 weeks

| **End point values** | Biomarker-High, Placebo | Biomarker-High, Lebrikizumab 37.5 mg | Biomarker-High, Lebrikizumab 125 mg | Biomarker-Low, Placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 247 | 257 | 251 | 107 |
| Units: Weeks | | | | |
| median (confidence interval 95%) | 9999 (9999 to 9999) | 9999 (9999 to 9999) | 9999 (9999 to 9999) | 9999 (9999 to 9999) |

| End point values | Biomarker-Low, Lebrikizumab 37.5 mg | Biomarker-Low, Lebrikizumab 125 mg | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 99 | 106 | | |
| Units: Weeks | | | | |
| median (confidence interval 95%) | 9999 (9999 to 9999) | 9999 (9999 to 9999) | | |

**Statistical analyses**

| Statistical analysis title | High: Lebrikizumab 125 mg vs Placebo |
|---|---|

Statistical analysis description:

Hazard ratios were estimated by Cox regression with the following baseline covariates included as stratification factors: number of asthma exacerbations within the last 12 months, baseline asthma medications, geographic region and a 3-level categorical variable (periostin high and eosinophil high, periostin high and eosinophil low, periostin low and eosinophil high).

| | |
|---|---|
| Comparison groups | Biomarker-High, Placebo v Biomarker-High, Lebrikizumab 125 mg |
| Number of subjects included in analysis | 498 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0466 |
| Method | Cox regression |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.73 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.53 |
| upper limit | 1 |

| Statistical analysis title | High: Lebrikizumab 37.5 mg vs Placebo |
|---|---|

Statistical analysis description:

Hazard ratios were estimated by Cox regression with the following baseline covariates included as stratification factors: number of asthma exacerbations within the last 12 months, baseline asthma medications, geographic region and a 3-level categorical variable (periostin high and eosinophil high, periostin high and eosinophil low, periostin low and eosinophil high).

| | |
|---|---|
| Comparison groups | Biomarker-High, Placebo v Biomarker-High, Lebrikizumab 37.5 mg |

| | |
|---|---|
| Number of subjects included in analysis | 504 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0987 |
| Method | Cox regression |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.76 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.56 |
| upper limit | 1.05 |

| **Statistical analysis title** | Low: Lebrikizumab 125 mg vs Placebo |
|---|---|

Statistical analysis description:

Hazard ratios were estimated by Cox regression with the following baseline covariates included as stratification factors: number of asthma exacerbations within the last 12 months, baseline asthma medications and geographic region.

| | |
|---|---|
| Comparison groups | Biomarker-Low, Placebo v Biomarker-Low, Lebrikizumab 125 mg |
| Number of subjects included in analysis | 213 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8502 |
| Method | Cox regression |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 1.65 |

| **Statistical analysis title** | Low: Lebrikizumab 37.5 mg vs Placebo |
|---|---|

Statistical analysis description:

Hazard ratios were estimated by Cox regression with the following baseline covariates included as stratification factors: number of asthma exacerbations within the last 12 months, baseline asthma medications and geographic region.

| | |
|---|---|
| Comparison groups | Biomarker-Low, Placebo v Biomarker-Low, Lebrikizumab 37.5 mg |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2558 |
| Method | Cox regression |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.37 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 2.36 |

## Secondary: Rate of Urgent Asthma-Related Health Care Utilization (HCU) During the Placebo-Controlled Period

| End point title | Rate of Urgent Asthma-Related Health Care Utilization (HCU) During the Placebo-Controlled Period |
|---|---|

End point description:

Urgent health care utilization was defined as hospitalisations, emergency department visits, and acute care visits. Reported is the rate of urgent asthma-related health care utilization during the 52-week placebo-controlled period. ITT population included all subjects randomised in the study.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline up to Week 52

| End point values | Biomarker-High, Placebo | Biomarker-High, Lebrikizumab 37.5 mg | Biomarker-High, Lebrikizumab 125 mg | Biomarker-Low, Placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 247 | 257 | 251 | 107 |
| Units: HCU event rate | | | | |
| number (not applicable) | 0.45 | 0.35 | 0.42 | 0.30 |

| End point values | Biomarker-Low, Lebrikizumab 37.5 mg | Biomarker-Low, Lebrikizumab 125 mg | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 99 | 106 | | |
| Units: HCU event rate | | | | |
| number (not applicable) | 0.56 | 0.40 | | |

### Statistical analyses

| Statistical analysis title | High: Lebrikizumab 125 mg vs Placebo |
|---|---|

Statistical analysis description:

Adjusted health care utilization rates and rate ratios are estimates from a Poisson regression model with over-dispersion and adjusted for the following covariates in addition to log(patient years) as an offset: number of asthma exacerbations within the last 12 months, baseline asthma medications, geographic region and a 3-level categorical variable (periostin high and eosinophil high, periostin high and eosinophil low, periostin low and eosinophil high).

| | |
|---|---|
| Comparison groups | Biomarker-High, Placebo v Biomarker-High, Lebrikizumab 125 mg |
| Number of subjects included in analysis | 498 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7394 |
| Method | Poisson regression |
| Parameter estimate | Rate Ratio |
| Point estimate | 0.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.62 |
| upper limit | 1.41 |

| **Statistical analysis title** | High: Lebrikizumab 37.5 mg vs Placebo |
|---|---|

Statistical analysis description:

Adjusted health care utilization rates and rate ratios are estimates from a Poisson regression model with over-dispersion and adjusted for the following covariates in addition to log(patient years) as an offset: number of asthma exacerbations within the last 12 months, baseline asthma medications, geographic region and a 3-level categorical variable (periostin high and eosinophil high, periostin high and eosinophil low, periostin low and eosinophil high).

| | |
|---|---|
| Comparison groups | Biomarker-High, Placebo v Biomarker-High, Lebrikizumab 37.5 mg |
| Number of subjects included in analysis | 504 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2612 |
| Method | Poisson regression |
| Parameter estimate | Rate Ratio |
| Point estimate | 0.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 1.21 |

| **Statistical analysis title** | Low: Lebrikizumab 125 mg vs Placebo |
|---|---|

Statistical analysis description:

Adjusted health care utilization rates and rate ratios are estimates from a Poisson regression model with over-dispersion and adjusted for the following covariates in addition to log(patient years) as an offset: number of asthma exacerbations within the last 12 months, baseline asthma medications and geographic region.

| | |
|---|---|
| Comparison groups | Biomarker-Low, Placebo v Biomarker-Low, Lebrikizumab 125 mg |

| | |
|---|---|
| Number of subjects included in analysis | 213 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4049 |
| Method | Poisson regression |
| Parameter estimate | Rate Ratio |
| Point estimate | 1.35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 2.71 |

| **Statistical analysis title** | Low: Lebrikizumab 37.5 mg vs Placebo |
|---|---|

Statistical analysis description:

Adjusted health care utilization rates and rate ratios are estimates from a Poisson regression model with over-dispersion and adjusted for the following covariates in addition to log(patient years) as an offset: number of asthma exacerbations within the last 12 months, baseline asthma medications and geographic region.

| | |
|---|---|
| Comparison groups | Biomarker-Low, Placebo v Biomarker-Low, Lebrikizumab 37.5 mg |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0553 |
| Method | Poisson regression |
| Parameter estimate | Rate Ratio |
| Point estimate | 1.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.99 |
| upper limit | 3.65 |

## Secondary: Change From Baseline in Standardized Asthma Quality of Life Questionnaire (AQLQ ) Score at Week 52

| End point title | Change From Baseline in Standardized Asthma Quality of Life Questionnaire (AQLQ ) Score at Week 52 |
|---|---|

End point description:

Asthma-specific health-related quality of life was assessed by the overall score of the Standardized AQLQ. The AQLQ is a self-administered test with 32 questions; each with seven possible answers ranging from 1 to 7 with a higher score being more favourable. Total score is calculated as follows: sum of items 1to 32 divided by 32 for a score range of 1 to 7 with a higher score indicating a better outcome. Reported is the change in AQLQ score from baseline to the end of the placebo-controlled period at Week 52. ITT population included all subjects randomised in the study.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline, Week 52

| End point values | Biomarker-High, Placebo | Biomarker-High, Lebrikizumab 37.5 mg | Biomarker-High, Lebrikizumab 125 mg | Biomarker-Low, Placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 226 | 240 | 229 | 93 |
| Units: Score on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=246,256,249,106,99,106) | 4.06 (± 0.98) | 4.13 (± 0.98) | 4.09 (± 0.94) | 4.21 (± 1.07) |
| Change at Week 52 (n=226,240,229,93,87,96) | 0.83 (± 1.03) | 0.81 (± 1.06) | 1.06 (± 1.11) | 0.63 (± 1.07) |

| End point values | Biomarker-Low, Lebrikizumab 37.5 mg | Biomarker-Low, Lebrikizumab 125 mg | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 87 | 96 | | |
| Units: Score on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=246,256,249,106,99,106) | 4.08 (± 1.02) | 3.98 (± 0.98) | | |
| Change at Week 52 (n=226,240,229,93,87,96) | 0.80 (± 1.11) | 0.68 (± 1.00) | | |

## Statistical analyses

| Statistical analysis title | High: Lebrikizumab 125 mg vs Placebo |
|---|---|

Statistical analysis description:

Estimates are based on a MMRM analysis with an unstructured covariance matrix. Model used absolute change from baseline in AQLQ(S) score as response variable and included terms for treatment, visit, treatment visit, baseline AQLQ(S), baseline AQLQ(S) visit, number of asthma exacerbations within last 12 months, baseline asthma medications, geographic region and a 3-level categorical variable (periostin high, eosinophil high, periostin high, eosinophil low, periostin low, eosinophil high).

| | |
|---|---|
| Comparison groups | Biomarker-High, Placebo v Biomarker-High, Lebrikizumab 125 mg |
| Number of subjects included in analysis | 455 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0057 |
| Method | Mixed Model Repeated Measures (MMRM) |
| Parameter estimate | Difference in Adjusted Mean |
| Point estimate | 0.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.07 |
| upper limit | 0.43 |

| | |
|---|---|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.091 |

| **Statistical analysis title** | High: Lebrikizumab 37.5 mg vs Placebo |
|---|---|

Statistical analysis description:

Estimates are based on a MMRM analysis with an unstructured covariance matrix. Model used absolute change from baseline in AQLQ(S) score as response variable and included terms for treatment, visit, treatment visit, baseline AQLQ(S), baseline AQLQ(S) visit, number of asthma exacerbations within last 12 months, baseline asthma medications, geographic region and a 3-level categorical variable (periostin high, eosinophil high, periostin high, eosinophil low, periostin low, eosinophil high).

| | |
|---|---|
| Comparison groups | Biomarker-High, Placebo v Biomarker-High, Lebrikizumab 37.5 mg |
| Number of subjects included in analysis | 466 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9227 |
| Method | Mixed Model Repeated Measures (MMRM) |
| Parameter estimate | Difference in Adjusted Mean |
| Point estimate | 0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.17 |
| upper limit | 0.19 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.091 |

| **Statistical analysis title** | Low: Lebrikizumab 125 mg vs Placebo |
|---|---|

Statistical analysis description:

Estimates are based on a MMRM analysis with an unstructured covariance matrix. Model used absolute change from baseline in AQLQ(S) score as response variable and included terms for treatment, visit, treatment visit, baseline AQLQ(S), baseline AQLQ(S) visit, number of asthma exacerbations within last 12 months, baseline asthma medications and geographic region.

| | |
|---|---|
| Comparison groups | Biomarker-Low, Placebo v Biomarker-Low, Lebrikizumab 125 mg |
| Number of subjects included in analysis | 189 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5859 |
| Method | Mixed Model Repeated Measures (MMRM) |
| Parameter estimate | Difference in Adjusted Mean |
| Point estimate | -0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.36 |
| upper limit | 0.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.143 |

| **Statistical analysis title** | Low: Lebrikizumab 37.5 mg vs Placebo |
|---|---|
| Statistical analysis description: | |
| Estimates are based on a MMRM analysis with an unstructured covariance matrix. Model used absolute change from baseline in AQLQ(S) score as response variable and included terms for treatment, visit, treatment visit, baseline AQLQ(S), baseline AQLQ(S) visit, number of asthma exacerbations within last 12 months, baseline asthma medications and geographic region. | |
| Comparison groups | Biomarker-Low, Placebo v Biomarker-Low, Lebrikizumab 37.5 mg |
| Number of subjects included in analysis | 180 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4807 |
| Method | Mixed Model Repeated Measures (MMRM) |
| Parameter estimate | Difference in Adjusted Mean |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.18 |
| upper limit | 0.39 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.146 |

| **Secondary: Change from Baseline In Asthma Rescue Medication at Week 52** | |
|---|---|
| End point title | Change from Baseline In Asthma Rescue Medication at Week 52 |
| End point description: | |
| Reported here is the change in the number of puffs or nebulized treatments of asthma rescue medication from baseline to the end of the placebo-controlled period at Week 52. ITT population included all subjects randomised in the study. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 52 | |

| **End point values** | Biomarker-High, Placebo | Biomarker-High, Lebrikizumab 37.5 mg | Biomarker-High, Lebrikizumab 125 mg | Biomarker-Low, Placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 222 | 238 | 225 | 90 |
| Units: Puffs per day | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=247,256,250,107,99,105) | 3.0 (± 3.0) | 3.0 (± 3.5) | 3.5 (± 4.5) | 3.0 (± 3.0) |
| Change at Week 52 (n=222,238,225,90,83,93) | -0.4 (± 2.8) | -1.0 (± 2.4) | -1.2 (± 3.0) | -0.3 (± 2.0) |

| End point values | Biomarker-Low, Lebrikizumab 37.5 mg | Biomarker-Low, Lebrikizumab 125 mg | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 83 | 93 | | |
| Units: Puffs per day | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=247,256,250,107,99,105) | 2.9 (± 2.4) | 2.7 (± 2.3) | | |
| Change at Week 52 (n=222,238,225,90,83,93) | -0.7 (± 1.6) | -0.5 (± 1.5) | | |

## Statistical analyses

| Statistical analysis title | High: Lebrikizumab 125 mg vs Placebo |
|---|---|

Statistical analysis description:

Estimates are based on MMRM analysis with an unstructured covariance matrix. Model used absolute change from baseline in asthma rescue medication use as response variable and included terms for treatment, visit, treatment visit, baseline rescue medication use/visit, number of asthma exacerbations within last 12 months, baseline asthma medications, geographic region and 3-level categorical variable (periostin high, eosinophil high, periostin high, eosinophil low, periostin low, eosinophil high).

| | |
|---|---|
| Comparison groups | Biomarker-High, Placebo v Biomarker-High, Lebrikizumab 125 mg |
| Number of subjects included in analysis | 447 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0099 |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Difference in Adjusted Means |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | -0.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.2 |

| Statistical analysis title | High: Lebrikizumab 37.5 mg vs Placebo |
|---|---|

Statistical analysis description:

Estimates are based on MMRM analysis with an unstructured covariance matrix. Model used absolute change from baseline in asthma rescue medication use as response variable and included terms for treatment, visit, treatment visit, baseline rescue medication use/visit, number of asthma exacerbations within last 12 months, baseline asthma medications, geographic region and 3-level categorical variable (periostin high, eosinophil high, periostin high, eosinophil low, periostin low, eosinophil high).

| | |
|---|---|
| Comparison groups | Biomarker-High, Placebo v Biomarker-High, Lebrikizumab 37.5 mg |

| | |
|---|---|
| Number of subjects included in analysis | 460 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0451 |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Difference in Adjusted Means |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 0 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.2 |

| **Statistical analysis title** | Low: Lebrikizumab 125 mg vs Placebo |
|---|---|

Statistical analysis description:

Estimates are based on MMRM analysis with an unstructured covariance matrix. Model used absolute change from baseline in asthma rescue medication use as response variable and included terms for treatment, visit, treatment visit, baseline rescue medication use/visit, number of asthma exacerbations within last 12 months, baseline asthma medications and geographic region.

| | |
|---|---|
| Comparison groups | Biomarker-Low, Placebo v Biomarker-Low, Lebrikizumab 125 mg |
| Number of subjects included in analysis | 183 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5236 |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Difference in Adjusted Means |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.6 |
| upper limit | 0.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.2 |

| **Statistical analysis title** | Low: Lebrikizumab 37.5 mg vs Placebo |
|---|---|

Statistical analysis description:

Estimates are based on MMRM analysis with an unstructured covariance matrix. Model used absolute change from baseline in asthma rescue medication use as response variable and included terms for treatment, visit, treatment visit, baseline rescue medication use/visit, number of asthma exacerbations within last 12 months, baseline asthma medications and geographic region.

| | |
|---|---|
| Comparison groups | Biomarker-Low, Placebo v Biomarker-Low, Lebrikizumab 37.5 mg |

| | |
|---|---|
| Number of subjects included in analysis | 173 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1851 |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Difference in Adjusted Means |
| Point estimate | -0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | 0.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.2 |

## Secondary: Change From Baseline in Asthma Control Questionnaire-5 (ACQ-5 ) Score at Week 52

| | |
|---|---|
| End point title | Change From Baseline in Asthma Control Questionnaire-5 (ACQ-5 ) Score at Week 52 |

End point description:

The ACQ-5 is test with 5 questions; each with seven possible answers ranging from 0 to 6 with a lower score being more favourable. Total score range is 0 to 30 with a lower score indicating a better outcome. Reported is the change in ACQ-5 score from baseline to the end of the placebo-controlled period at Week 52. ITT population included all subjects randomised in the study.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline, Week 52

| End point values | Biomarker-High, Placebo | Biomarker-High, Lebrikizumab 37.5 mg | Biomarker-High, Lebrikizumab 125 mg | Biomarker-Low, Placebo |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 224 | 240 | 230 | 93 |
| Units: Score on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=246,256,250,106,99,106) | 2.8 (± 0.7) | 2.7 (± 0.7) | 2.7 (± 0.7) | 2.7 (± 0.7) |
| Change at Week 52 (n=224,240,230,93,87,96) | -0.8 (± 1.0) | -0.8 (± 1.0) | -1.0 (± 1.1) | -0.7 (± 0.9) |

| End point values | Biomarker-Low, Lebrikizumab 37.5 mg | Biomarker-Low, Lebrikizumab 125 mg | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 87 | 96 | | |
| Units: Score on scale | | | | |

| arithmetic mean (standard deviation) | | | | |
|---|---|---|---|---|
| Baseline (n=246,256,250,106,99,106) | 2.8 (± 0.8) | 2.8 (± 0.7) | | |
| Change at Week 52 (n=224,240,230,93,87,96) | -0.8 (± 1.0) | -0.7 (± 1.0) | | |

## Statistical analyses

| **Statistical analysis title** | High: Lebrikizumab 125 mg vs Placebo |
|---|---|

Statistical analysis description:

Estimates are based on MMRM analysis with an unstructured covariance matrix. Model used absolute change from baseline in ACQ-5 as response variable and included terms for treatment, visit, treatment visit, baseline ACQ-5, baseline ACQ-5 visit, number of asthma exacerbations within the last 12 months, baseline asthma medications, geographic region and 3-level categorical variable (periostin high, eosinophil high, periostin high, eosinophil low, periostin low,eosinophil high).

| Comparison groups | Biomarker-High, Placebo v Biomarker-High, Lebrikizumab 125 mg |
|---|---|
| Number of subjects included in analysis | 454 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.097 |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Difference in Adjusted Mean |
| Point estimate | -0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3 |
| upper limit | 0 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.09 |

| **Statistical analysis title** | High: Lebrikizumab 37.5 mg vs Placebo |
|---|---|

Statistical analysis description:

Estimates are based on MMRM analysis with an unstructured covariance matrix. Model used absolute change from baseline in ACQ-5 as response variable and included terms for treatment, visit, treatment visit, baseline ACQ-5, baseline ACQ-5 visit, number of asthma exacerbations within the last 12 months, baseline asthma medications, geographic region and 3-level categorical variable (periostin high, eosinophil high, periostin high, eosinophil low, periostin low,eosinophil high).

| Comparison groups | Biomarker-High, Placebo v Biomarker-High, Lebrikizumab 37.5 mg |
|---|---|
| Number of subjects included in analysis | 464 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9071 |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Difference in Adjusted Mean |
| Point estimate | 0 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.2 |
| upper limit | 0.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.09 |

| **Statistical analysis title** | Low: Lebrikizumab 125 mg vs Placebo |
|---|---|

Statistical analysis description:

Estimates are based on MMRM analysis with an unstructured covariance matrix. Model used absolute change from baseline in ACQ-5 as response variable and included terms for treatment, visit, treatment visit, baseline ACQ-5, baseline ACQ-5 visit, number of asthma exacerbations within the last 12 months, baseline asthma medications and geographic region.

| | |
|---|---|
| Comparison groups | Biomarker-Low, Placebo v Biomarker-Low, Lebrikizumab 125 mg |
| Number of subjects included in analysis | 189 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8885 |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Difference in Adjusted Mean |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.2 |
| upper limit | 0.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.13 |

| **Statistical analysis title** | Low: Lebrikizumab 37.5 mg vs Placebo |
|---|---|

Statistical analysis description:

Estimates are based on MMRM analysis with an unstructured covariance matrix. Model used absolute change from baseline in ACQ-5 as response variable and included terms for treatment, visit, treatment visit, baseline ACQ-5, baseline ACQ-5 visit, number of asthma exacerbations within the last 12 months, baseline asthma medications and geographic region.

| | |
|---|---|
| Comparison groups | Biomarker-Low, Placebo v Biomarker-Low, Lebrikizumab 37.5 mg |
| Number of subjects included in analysis | 180 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3466 |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | Difference in Adjusted Mean |
| Point estimate | -0.1 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 0.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.14 |

## Secondary: Percentage of Subjects With Adverse Events

| | |
|---|---|
| End point title | Percentage of Subjects With Adverse Events |

End point description:

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. The safety population included all subjects who received at least one dose of study medication.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline, Week 124

| End point values | Placebo | Placebo/Lebrikizumab (37.5 mg) | Placebo/Lebrikizumab (125 mg) | Lebrikizumab (37.5 mg) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 44[1] | 155 | 154 | 356 |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 71.1 | 90.3 | 85.1 | 82.0 |

Notes:

[1] - Safety population actual n=45 due to transfer of subject from other arm.

| End point values | Lebrikizumab (125 mg) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 357 | | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 83.2 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Anti-Therapeutic Antibodies to Lebrikizumab

| | |
|---|---|
| End point title | Percentage of Subjects With Anti-Therapeutic Antibodies to |

| | |
|---|---|
| | Lebrikizumab |

End point description:

The safety population included all subjects who received at least one dose of study medication.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline up to Week 124 (assessed at Baseline, Weeks 4, 12, 24, 36, 52 and Safety Follow-up Week 20 [or end of the study])

| **End point values** | Placebo | Placebo/Lebrikizumab (37.5 mg) | Placebo/Lebrikizumab (125 mg) | Lebrikizumab (37.5 mg) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 44[2] | 155 | 154 | 354 |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 0 | 11.6 | 8.4 | 16.1 |

Notes:

[2] - Safety population n=45 for this arm due to transfer from other arm.

| **End point values** | Lebrikizumab (125 mg) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 356 | | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 14.0 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Minimum Serum Concentration (Cmin ) of Lebrikizumab

| | |
|---|---|
| End point title | Minimum Serum Concentration (Cmin ) of Lebrikizumab[3] |

End point description:

ITT population included all subjects randomised in the study. 9999 = not reportable (when more than one third of values were lower than reportable, which was set to 0.045 mcg/mL).

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Predose (0 hour) at Weeks 4, 12, 24, 36, and 52

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Minimum serum concentration of Lebrikizumab was only measured in the arm that received lebrikizumab treatment. Therefore, data are only reported for the lebrikizumab arm.

| End point values | Lebrikizumab (37.5 mg) | Lebrikizumab (125 mg) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 348 | 344 | | |
| Units: microgram per millilitre (mcg/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=1, 0, 348, 344) | 2.74 (± 2.25) | 8.67 (± 3.82) | | |
| Week 12 (n=0, 1, 339, 342) | 4.44 (± 2.96) | 15.5 (± 6.60) | | |
| Week 24 (n=0, 0, 327, 335) | 4.28 (± 3.06) | 16.0 (± 7.73) | | |
| Week 36 (n=0, 2, 325, 322) | 4.51 (± 2.81) | 17.0 (± 8.86) | | |
| Week 52 (n=0, 0, 320, 314) | 4.59 (± 3.15) | 17.3 (± 8.80) | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Up to 124 weeks | |
| Adverse event reporting additional description: | |
| Safety population included all subjects who received at least one dose of study medication. | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19.1 |

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects received SC injection of lebrikizumab matching placebo every 4 weeks for 52 weeks during the placebo-controlled period. Subjects then completed a 20-week safety follow-up. | |
| Reporting group title | Placebo/Lebrikizumab (37.5 mg) |
| Reporting group description: | |
| Subjects received SC injection of lebrikizumab matching placebo every 4 weeks for 52 weeks during the placebo-controlled period and then SC injection of lebrikizumab at 37.5 mg for 52 weeks during the active treatment extension period. After study treatment, subjects completed a 20-week safety follow-up. | |
| Reporting group title | Placebo/Lebrikizumab (125 mg) |
| Reporting group description: | |
| Subjects received SC injection of lebrikizumab matching placebo every 4 weeks for 52 weeks during the placebo-controlled period and then SC injection of lebrikizumab at 125 mg for 52 weeks during active treatment extension period. After study treatment, subjects completed a 20-week safety follow-up. | |
| Reporting group title | Lebrikizumab (37.5 mg) |
| Reporting group description: | |
| Subjects received SC injection of lebrikizumab (37.5 mg) every 4 weeks for 104 weeks. After study treatment, subjects completed a 20-week safety follow-up. | |
| Reporting group title | Lebrikizumab (125 mg) |
| Reporting group description: | |
| Subjects received SC injection of lebrikizumab (125 milligrams [mg]) every 4 weeks for 104 weeks. After study treatment, subjects completed a 20-week safety follow-up. | |

| Serious adverse events | Placebo | Placebo/Lebrikizumab (37.5 mg) | Placebo/Lebrikizumab (125 mg) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 11 / 45 (24.44%) | 22 / 155 (14.19%) | 24 / 154 (15.58%) |
| number of deaths (all causes) | 0 | 0 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 155 (0.65%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Colon cancer | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder neoplasm | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bowen's disease | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometrial cancer | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 155 (0.00%) | 0 / 154 (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 |
| Gastric cancer | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lipoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to lung | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine cancer | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 155 (0.00%) | 0 / 154 (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 |
| Vocal cord neoplasm | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 155 (0.00%) | 0 / 154 (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 |
| Vascular disorders | | | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jugular vein thrombosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subclavian vein thrombosis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Varicose vein | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Abortion induced | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abortion threatened | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ectopic pregnancy | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Imminent abortion | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 1 / 155 (0.65%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthenia | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 155 (0.00%) | 0 / 154 (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 |
| Cyst | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sarcoidosis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Uterine prolapse | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometrial hyperplasia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 5 / 45 (11.11%) | 8 / 155 (5.16%) | 4 / 154 (2.60%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 15 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 2 / 45 (4.44%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 155 (0.65%) | 0 / 154 (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 |
| Dysphonia | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 155 (0.00%) | 0 / 154 (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 |
| Eosinophilic pneumonia | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 155 (0.00%) | 0 / 154 (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 |
| Hydrothorax | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal polyps | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngeal inflammation | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary hilar enlargement | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Status asthmaticus | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 155 (0.65%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Acute psychosis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Completed suicide | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Depression suicidal | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hallucination | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 155 (0.00%) | 0 / 154 (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 |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood pressure increased | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 155 (0.65%) | 0 / 154 (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 | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest injury | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fibula fracture | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 155 (0.65%) | 0 / 154 (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 |
| Overdose | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Patella fracture | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road traffic accident | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Scapula fracture | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 155 (0.65%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| 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 unstable | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 155 (0.00%) | 0 / 154 (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 failure congestive | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 155 (0.00%) | 0 / 154 (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 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiomyopathy | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 155 (0.00%) | 0 / 154 (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 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery insufficiency | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 155 (0.65%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Palpitations | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 155 (0.65%) | 0 / 154 (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 |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 155 (0.00%) | 0 / 154 (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 |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 155 (0.00%) | 0 / 154 (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 |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Memory impairment | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myoclonus | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 155 (0.00%) | 0 / 154 (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 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pschyogenic pseudosyncope | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Aplastic anaemia | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eosinophilia | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| 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 | | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 2 / 155 (1.29%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal hernia | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dental cyst | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric perforation | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 155 (0.65%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia strangulated | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine polyp | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Obstruction gastric | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Hepatobiliary disorders** | | | |
| Bile duct stone | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 155 (0.65%) | 0 / 154 (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 |
| Biliary colic | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Skin and subcutaneous tissue disorders** | | | |
| Angioedema | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 155 (0.00%) | 0 / 154 (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 |
| Pyoderma gangrenosum | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Renal and urinary disorders** | | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal colic | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc displacement | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 2 / 155 (1.29%) | 0 / 154 (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 |
| Influenza | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 155 (0.00%) | 0 / 154 (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 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 155 (0.65%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rhinovirus infection | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 155 (0.00%) | 0 / 154 (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 |
| Tuberculosis | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 155 (0.00%) | 0 / 154 (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 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glucose tolerance impaired | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 155 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Lebrikizumab (37.5 mg) | Lebrikizumab (125 mg) | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 56 / 356 (15.73%) | 57 / 357 (15.97%) | |
| number of deaths (all causes) | 1 | 1 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder neoplasm | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bowen's disease | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Endometrial cancer | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric cancer | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Lipoma | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to lung | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine cancer | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vocal cord neoplasm | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |

| | | | |
|---|---|---|---|
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 2 / 357 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subclavian vein thrombosis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Varicose vein | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Abortion induced | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 2 / 356 (0.56%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abortion threatened | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Ectopic pregnancy | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Imminent abortion | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cyst | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sarcoidosis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Reproductive system and breast disorders | | | |
| Uterine prolapse | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometrial hyperplasia | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 18 / 356 (5.06%) | 19 / 357 (5.32%) | |
| occurrences causally related to treatment / all | 0 / 25 | 0 / 23 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eosinophilic pneumonia | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrothorax | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasal polyps | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngeal inflammation | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary hilar enlargement | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Status asthmaticus | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Acute psychosis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Completed suicide | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression suicidal | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hallucination | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood pressure increased | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Foot fracture | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 2 / 357 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest injury | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fibula fracture | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hand fracture | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overdose | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Patella fracture | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tibia fracture | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Scapula fracture | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiomyopathy | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery insufficiency | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery occlusion | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 2 / 356 (0.56%) | 2 / 357 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Memory impairment | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myoclonus | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pschyogenic pseudosyncope | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Aplastic anaemia | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eosinophilia | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukocytosis | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 2 / 356 (0.56%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 2 / 357 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal hernia | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dental cyst | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric perforation | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia strangulated | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine polyp | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstruction gastric | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Biliary colic | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|---|---|---|
| Angioedema | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyoderma gangrenosum | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal colic | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc displacement | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 5 / 356 (1.40%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 2 / 357 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhinovirus infection | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tuberculosis | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|---|---|---|
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 357 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Glucose tolerance impaired | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 357 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | Placebo | Placebo/Lebrikizumab (37.5 mg) | Placebo/Lebrikizumab (125 mg) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 24 / 45 (53.33%) | 117 / 155 (75.48%) | 118 / 154 (76.62%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 13 / 155 (8.39%) | 12 / 154 (7.79%) |
| occurrences (all) | 0 | 19 | 16 |
| General disorders and administration site conditions | | | |
| Injection site pain | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | 7 / 155 (4.52%) | 5 / 154 (3.25%) |
| occurrences (all) | 11 | 44 | 21 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 13 / 155 (8.39%) | 3 / 154 (1.95%) |
| occurrences (all) | 0 | 13 | 3 |
| Nausea | | | |
| subjects affected / exposed | 2 / 45 (4.44%) | 8 / 155 (5.16%) | 1 / 154 (0.65%) |
| occurrences (all) | 2 | 12 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| Asthma | | | |
| subjects affected / exposed | 14 / 45 (31.11%) | 73 / 155 (47.10%) | 75 / 154 (48.70%) |
| occurrences (all) | 23 | 177 | 211 |
| Cough | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | 8 / 155 (5.16%) | 8 / 154 (5.19%) |
| occurrences (all) | 5 | 11 | 10 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 3 / 155 (1.94%) | 8 / 154 (5.19%) |
| occurrences (all) | 1 | 3 | 8 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 6 / 155 (3.87%) | 14 / 154 (9.09%) |
| occurrences (all) | 2 | 7 | 17 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 10 / 155 (6.45%) | 9 / 154 (5.84%) |
| occurrences (all) | 1 | 12 | 10 |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 11 / 155 (7.10%) | 4 / 154 (2.60%) |
| occurrences (all) | 1 | 12 | 4 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 6 / 45 (13.33%) | 30 / 155 (19.35%) | 41 / 154 (26.62%) |
| occurrences (all) | 10 | 47 | 66 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 6 / 45 (13.33%) | 23 / 155 (14.84%) | 28 / 154 (18.18%) |
| occurrences (all) | 9 | 35 | 51 |
| Bronchitis | | | |
| subjects affected / exposed | 4 / 45 (8.89%) | 19 / 155 (12.26%) | 22 / 154 (14.29%) |
| occurrences (all) | 5 | 26 | 30 |
| Sinusitis | | | |
| subjects affected / exposed | 2 / 45 (4.44%) | 13 / 155 (8.39%) | 15 / 154 (9.74%) |
| occurrences (all) | 4 | 31 | 34 |
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 45 (4.44%) | 8 / 155 (5.16%) | 8 / 154 (5.19%) |
| occurrences (all) | 2 | 8 | 12 |
| Urinary tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 45 (2.22%) | 4 / 155 (2.58%) | 6 / 154 (3.90%) |
| occurrences (all) | 1 | 5 | 6 |
| Acute sinusitis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 10 / 155 (6.45%) | 7 / 154 (4.55%) |
| occurrences (all) | 0 | 14 | 16 |
| Influenza | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 6 / 155 (3.87%) | 9 / 154 (5.84%) |
| occurrences (all) | 0 | 6 | 9 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 4 / 155 (2.58%) | 5 / 154 (3.25%) |
| occurrences (all) | 0 | 5 | 8 |

| **Non-serious adverse events** | Lebrikizumab (37.5 mg) | Lebrikizumab (125 mg) | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 239 / 356 (67.13%) | 249 / 357 (69.75%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 29 / 356 (8.15%) | 39 / 357 (10.92%) | |
| occurrences (all) | 47 | 77 | |
| General disorders and administration site conditions | | | |
| Injection site pain | | | |
| subjects affected / exposed | 13 / 356 (3.65%) | 16 / 357 (4.48%) | |
| occurrences (all) | 144 | 92 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 18 / 356 (5.06%) | 13 / 357 (3.64%) | |
| occurrences (all) | 22 | 14 | |
| Nausea | | | |
| subjects affected / exposed | 9 / 356 (2.53%) | 12 / 357 (3.36%) | |
| occurrences (all) | 9 | 13 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 148 / 356 (41.57%) | 146 / 357 (40.90%) | |
| occurrences (all) | 412 | 376 | |
| Cough | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 18 / 356 (5.06%) | 21 / 357 (5.88%) | |
| occurrences (all) | 36 | 23 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 11 / 356 (3.09%) | 8 / 357 (2.24%) | |
| occurrences (all) | 11 | 9 | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 9 / 356 (2.53%) | 13 / 357 (3.64%) | |
| occurrences (all) | 11 | 17 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 20 / 356 (5.62%) | 19 / 357 (5.32%) | |
| occurrences (all) | 22 | 21 | |
| Arthralgia | | | |
| subjects affected / exposed | 24 / 356 (6.74%) | 17 / 357 (4.76%) | |
| occurrences (all) | 27 | 18 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 72 / 356 (20.22%) | 60 / 357 (16.81%) | |
| occurrences (all) | 120 | 101 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 52 / 356 (14.61%) | 64 / 357 (17.93%) | |
| occurrences (all) | 81 | 121 | |
| Bronchitis | | | |
| subjects affected / exposed | 44 / 356 (12.36%) | 33 / 357 (9.24%) | |
| occurrences (all) | 63 | 47 | |
| Sinusitis | | | |
| subjects affected / exposed | 28 / 356 (7.87%) | 20 / 357 (5.60%) | |
| occurrences (all) | 36 | 25 | |
| Pharyngitis | | | |
| subjects affected / exposed | 21 / 356 (5.90%) | 16 / 357 (4.48%) | |
| occurrences (all) | 25 | 20 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 18 / 356 (5.06%) | 14 / 357 (3.92%) | |
| occurrences (all) | 27 | 19 | |
| Acute sinusitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 14 / 356 (3.93%) | 13 / 357 (3.64%) | |
| occurrences (all) | 23 | 16 | |
| Influenza | | | |
| subjects affected / exposed | 16 / 356 (4.49%) | 8 / 357 (2.24%) | |
| occurrences (all) | 16 | 11 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 18 / 356 (5.06%) | 13 / 357 (3.64%) | |
| occurrences (all) | 27 | 14 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 10 September 2015 | The protocol was amended for the following reasons: 1) To update the description of completed clinical trials with lebrikizumab, 2) To add blood eosinophil count in the biomarker objective, 3) To add fractional exhaled nitric oxygen (FeNO) as an exploratory objective, 4) To update the biomarker subgroups for analysis to include blood eosinophil count. Biomarker-high subjects will be defined as subjects with baseline periostin ≥ 50 ng/mL or blood eosinophils ≥ 300 cells/µL, and biomarker-low subjects will be defined as subjects with baseline periostin < 50 ng/mL and blood eosinophils < 300 cells/µL, 5) To update the secondary efficacy endpoints and exploratory endpoints, 6) To update the Medical Monitor to reflect the current medical monitors, 6) To update details of the statistical analyses. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported