



Clinical trial results:

The Clinical Effectiveness of Fluticasone Furoate/Umeclidinium Bromide/Vilanterol in a Single Inhaler (TRELEGYTM ELLIPTATM) when Compared with Non-ELLIPTA Multiple Inhaler Triple Therapies in COPD Patients within a Usual Care Setting

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2017-004369-29 |
| Trial protocol | SE GB NL ES |
| Global end of trial date | 10 October 2019 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 04 September 2020 |
| First version publication date | 04 September 2020 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 206854 |
|-----------------------|--------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | GlaxoSmithKline |
| Sponsor organisation address | 980 Great West Road, Brentford, Middlesex, United Kingdom, |
| Public contact | GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com |
| Scientific contact | GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.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 | 17 December 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 10 October 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the effectiveness of TRELEGY ELLIPTA with non-ELLIPTA MITT for the impact of COPD on wellbeing and daily life after 24 weeks treatment.

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 11 April 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|----------------------|
| Country: Number of subjects enrolled | Germany: 871 |
| Country: Number of subjects enrolled | Netherlands: 638 |
| Country: Number of subjects enrolled | Spain: 264 |
| Country: Number of subjects enrolled | Sweden: 268 |
| Country: Number of subjects enrolled | United Kingdom: 1300 |
| Worldwide total number of subjects | 3341 |
| EEA total number of subjects | 3341 |

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) | 1148 |
| From 65 to 84 years | 2128 |

| | |
|-------------------|----|
| 85 years and over | 65 |
|-------------------|----|

Subject disposition

Recruitment

Recruitment details:

This was a Phase IV, open-label, randomized study to evaluate the effectiveness of TRELEGY ELLIPTA relative to non-ELLIPTA multiple inhaler triple therapies (MITT) for chronic obstructive pulmonary disease (COPD) control within the usual clinical practice setting. TRELEGY and ELLIPTA are registered trademarks of GlaxoSmithKline group of companies.

Pre-assignment

Screening details:

A total of 3341 participants were screened and 3109 participants (Par.) were enrolled in this study. Of which, 3092 participants were randomized and received the study treatment. The remaining 17 participants were randomized in error (those who were recorded as screen failures and also randomized) and did not receive investigational product (IP).

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI |

Arm description:

Eligible participants received a combination of fluticasone furoate (FF) blended with lactose in the first strip (100 microgram [mcg] per blister); and umeclidinium bromide (UMEC) and vilanterol (VI) blended with lactose and magnesium stearate in second strip (62.5 mcg UMEC per blister and 25 mcg VI per blister), a single inhalation once daily in the same TRELEGY ELLIPTA dry powder inhaler (DPI) via inhalation route for a period of 24 weeks. Participants were administered other prescribed COPD medications such as rescue medications according to usual practice, as suggested by physician.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Fluticasone furoate /Umeclidinium bromide/Vilanterol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

A combination of fluticasone furoate blended with lactose in the first strip (100 microgram [mcg] per blister) and umeclidinium bromide (UMEC) and vilanterol (VI) blended with lactose and magnesium stearate in second strip (62.5 mcg UMEC per blister and 25 mcg VI per blister), a single inhalation once daily in the same TRELEGY ELLIPTA dry powder inhaler via inhalation route for a period of 24 weeks.

| | |
|------------------|------------------|
| Arm title | Non-ELLIPTA MITT |
|------------------|------------------|

Arm description:

Eligible participants received the inhaled corticosteroid (ICS)/long-acting muscarinic receptor antagonist (LAMA)/long-acting beta agonist (LABA) products twice daily as prescribed by the physician for a period of 24 weeks. Participants were administered other prescribed COPD medications such as rescue medications according to usual practice, as suggested by physician.

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Non-ELLIPTA Multiple Inhaler Triple Therapies (MITT) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Inhaled corticosteroid/long-acting muscarinic receptor antagonist/long-acting beta agonist products twice daily as prescribed by the physician for a period of 24 weeks.

| Number of subjects in period 1^[1] | FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI | Non-ELLIPTA MITT |
|---|--|-------------------------|
| Started | 1545 | 1547 |
| Randomized but did not start IP | 1 ^[2] | 0 ^[3] |
| Completed IP | 1256 ^[4] | 1359 ^[5] |
| Not Completed IP | 288 ^[6] | 188 ^[7] |
| Withdrew IP (WIP): Lost to follow-up | 15 ^[8] | 24 ^[9] |
| WIP: Protocol deviation | 0 ^[10] | 2 ^[11] |
| WIP: Adverse event | 112 ^[12] | 29 ^[13] |
| WIP: Lack of efficacy | 56 ^[14] | 28 ^[15] |
| WIP: Physician Decision | 14 ^[16] | 27 ^[17] |
| WIP: Withdrawal by Participant | 91 ^[18] | 78 ^[19] |
| Completed | 1498 | 1493 |
| Not completed | 47 | 54 |
| Adverse event, serious fatal | 8 | 8 |
| Consent withdrawn by subject | 15 | 17 |
| Physician decision | 2 | 1 |
| Adverse event, non-fatal | 1 | 1 |
| Lost to follow-up | 18 | 25 |
| Lack of efficacy | 3 | 1 |
| Protocol deviation | - | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 3341 participants were screened and 3109 participants (Par.) were enrolled in this study. Of which, 3092 participants were randomized and received the study treatment. The remaining 17 participants were randomized in error (those who were recorded as screen failures and also randomized) and did not receive investigational product (IP).

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

Justification: This number indicates the number of participant randomized but did not start investigational product.

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

Justification: This number indicates the number of participant randomized but did not start investigational product.

completed, minus those who left.

Justification: This number indicates the number of participant randomized but did not start investigational product.

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

Justification: This number indicates the number of participant randomized but did not start investigational product.

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

Justification: This number indicates the number of participant randomized but did not start investigational product.

Baseline characteristics

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI |
|-----------------------|---|

Reporting group description:

Eligible participants received a combination of fluticasone furoate (FF) blended with lactose in the first strip (100 microgram [mcg] per blister); and umeclidinium bromide (UMEC) and vilanterol (VI) blended with lactose and magnesium stearate in second strip (62.5 mcg UMEC per blister and 25 mcg VI per blister), a single inhalation once daily in the same TRELEGY ELLIPTA dry powder inhaler (DPI) via inhalation route for a period of 24 weeks. Participants were administered other prescribed COPD medications such as rescue medications according to usual practice, as suggested by physician.

| | |
|-----------------------|------------------|
| Reporting group title | Non-ELLIPTA MITT |
|-----------------------|------------------|

Reporting group description:

Eligible participants received the inhaled corticosteroid (ICS)/long-acting muscarinic receptor antagonist (LAMA)/long-acting beta agonist (LABA) products twice daily as prescribed by the physician for a period of 24 weeks. Participants were administered other prescribed COPD medications such as rescue medications according to usual practice, as suggested by physician.

| Reporting group values | FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI | Non-ELLIPTA MITT | Total |
|---|---|------------------|-------|
| Number of subjects | 1545 | 1547 | 3092 |
| Age categorical Units: Subjects | | | |
| Total Participants | 1545 | 1547 | 3092 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 67.8 | 67.8 | - |
| standard deviation | ± 8.78 | ± 8.59 | |
| Sex: Female, Male Units: Participants | | | |
| Female | 708 | 729 | 1437 |
| Male | 837 | 818 | 1655 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Asian- Central/South Asian Heritage | 12 | 7 | 19 |
| Asian- East Asian Heritage | 0 | 1 | 1 |
| Asian- South East Asian Heritage | 1 | 6 | 7 |
| Black or African American | 3 | 4 | 7 |
| White- Arabic/North African Heritage | 6 | 7 | 13 |
| White- White/Caucasian/European Heritage | 1523 | 1521 | 3044 |
| White and Black or African American | 0 | 1 | 1 |

End points

End points reporting groups

| | |
|-----------------------|---|
| Reporting group title | FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI |
|-----------------------|---|

Reporting group description:

Eligible participants received a combination of fluticasone furoate (FF) blended with lactose in the first strip (100 microgram [mcg] per blister); and umecclidinium bromide (UMEC) and vilanterol (VI) blended with lactose and magnesium stearate in second strip (62.5 mcg UMEC per blister and 25 mcg VI per blister), a single inhalation once daily in the same TRELEGY ELLIPTA dry powder inhaler (DPI) via inhalation route for a period of 24 weeks. Participants were administered other prescribed COPD medications such as rescue medications according to usual practice, as suggested by physician.

| | |
|-----------------------|------------------|
| Reporting group title | Non-ELLIPTA MITT |
|-----------------------|------------------|

Reporting group description:

Eligible participants received the inhaled corticosteroid (ICS)/long-acting muscarinic receptor antagonist (LAMA)/long-acting beta agonist (LABA) products twice daily as prescribed by the physician for a period of 24 weeks. Participants were administered other prescribed COPD medications such as rescue medications according to usual practice, as suggested by physician.

Primary: Number of responders and non-responders based on the chronic obstructive pulmonary disease assessment test (CAT) at Week 24 and number of participants with imputed CAT score at Week 24

| | |
|-----------------|--|
| End point title | Number of responders and non-responders based on the chronic obstructive pulmonary disease assessment test (CAT) at Week 24 and number of participants with imputed CAT score at Week 24 |
|-----------------|--|

End point description:

The CAT is a 8-item questionnaire. Par. rated their experience as 0 (no impact) to 5 (maximum impact). CAT score was calculated by summing the non-missing scores of the 8 items with a range of 0-40 (higher scores: greater disease impact). Responders had a change from Baseline score ≥ 2 and non-responders had a change from Baseline score < 2 at Week 24. Change from Baseline was Week 24 value minus the Baseline value (Day 1). A composite strategy was applied when intercurrent events of randomized treatment modification, change in pulmonary rehabilitation or start of oxygen therapy occurred, otherwise a treatment policy strategy was applied. Missing Week 24 CAT data were imputed assuming missing at random. Intent-to-Treat (ITT) Population comprised of all randomized participants (who received a randomization number), excluding those who were randomized in error (a screen failure and also randomized). Only those participants with non-missing covariates were included in the analysis.

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

End point timeframe:

At Week 24

| End point values | FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI | Non-ELLIPTA MITT | | |
|-------------------------------------|--|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1539 ^[1] | 1543 ^[2] | | |
| Units: Participants | | | | |
| Responders | 731 | 616 | | |
| Non-responders | 756 | 835 | | |
| Participants with imputed CAT score | 52 | 92 | | |

Notes:

[1] - ITT Population

[2] - ITT Population

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| Statistical comparison is presented for combined data of responders, non-responders and those with imputed CAT score at Week 24. | |
| Comparison groups | FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI v Non-ELLIPTA MITT |
| Number of subjects included in analysis | 3082 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | < 0.001 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.13 |
| upper limit | 1.51 |

Notes:

[3] - Analysis was performed using logistic regression model with covariates of treatment group, Baseline CAT score, number of exacerbations in the prior year, actual prior medication use strata and country.

Secondary: Change from Baseline in forced expiratory volume in 1 second (FEV1) at Week 24

| | |
|---|--|
| End point title | Change from Baseline in forced expiratory volume in 1 second (FEV1) at Week 24 |
| End point description: | |
| FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. FEV1 measurements were collected using a spirometer. Baseline was defined as the value recorded at Day 1. Change from Baseline was calculated as FEV1 value at Week 24 minus the Baseline value. A treatment policy strategy was used for the intercurrent events of randomized treatment discontinuation, randomized treatment modification, change of pulmonary rehabilitation status and start of oxygen therapy. Only those participants with non-missing covariates were included in the analysis. FEV1 Population comprised of all participants of the ITT population for whom a spirometry assessment was performed at any of Visit 1 (Day 1) or Visit 2 (Week 24). Only those participants with data available at the specified data points were analyzed. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline (Day 1) and at Week 24 | |

| | | | | |
|-------------------------------------|---|--------------------|--|--|
| End point values | FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI | Non-ELLIPTA MITT | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 691 ^[4] | 675 ^[5] | | |
| Units: Liters | | | | |
| least squares mean (standard error) | 1.446 (± 0.0105) | 1.396 (± 0.0108) | | |

Notes:

[4] - FEV1 Population

[5] - FEV1 Population

Statistical analyses

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

Analysis was performed using an ANCOVA with covariates of treatment group, Baseline FEV1, actual prior medication use strata, country and timing of spirometry.

| | |
|---|--|
| Comparison groups | FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI v Non-ELLIPTA MITT |
| Number of subjects included in analysis | 1366 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.026 |
| upper limit | 0.073 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0121 |

Secondary: Percentage of participants making at least 1 critical error in inhalation technique at Week 24

| | |
|-----------------|--|
| End point title | Percentage of participants making at least 1 critical error in inhalation technique at Week 24 |
|-----------------|--|

End point description:

Participants were trained on the correct use of their inhaler devices. All participants who had spirometry measured were to have an assessment of inhaler errors. During the assessment, participants were asked to demonstrate inhaler use when taking their regular dose of medication. A critical error is defined as an error that is most likely to result in no or significantly reduced medication being inhaled. These errors were recorded in an error checklist, during the assessment. A hypothetical strategy was used for the intercurrent event of randomized treatment modification. Percentage of participants making at least 1 critical error in inhalation technique at the Week 24 is presented. Critical error Population comprised of all participants of the ITT population for whom a critical error assessment was performed at Visit 2 (Week 24). Only those participants with data available at the specified data points were analyzed.

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

End point timeframe:

At Week 24

| | | | | |
|-----------------------------------|--|---------------------|--|--|
| End point values | FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI | Non-ELLIPTA MITT | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 653 ^[6] | 230 ^[7] | | |
| Units: Percentage of Participants | 6 | 3 | | |

Notes:

[6] - Critical error Population

[7] - Critical error Population

Statistical analyses

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

Analysis was performed using logistic regression model with covariates of treatment group, actual prior medication use strata and country.

| | |
|---|---|
| Comparison groups | FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI v Non-ELLIPTA MITT |
| Number of subjects included in analysis | 883 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.103 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.87 |
| upper limit | 4.53 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious AEs (non-SAEs) were collected from the start of study treatment up to Week 24

Adverse event reporting additional description:

Data is reported for the ITT Population which comprised of all randomized participants (who received a randomization number), excluding those who were randomized in error. All SAEs were collected. Non-SAEs which were only drug-related or that lead to withdrawal from study/study treatment were collected.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 22.1 |

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | FF/UMEC/VI 100/62.5/25 |
|-----------------------|------------------------|

Reporting group description:

Eligible participants received a combination of fluticasone furoate (FF) blended with lactose in the first strip (100 microgram [mcg] per blister); and umeclidinium bromide (UMEC) and vilanterol (VI) blended with lactose and magnesium stearate in second strip (62.5 mcg UMEC per blister and 25 mcg VI per blister), a single inhalation once daily in the same TRELEGY ELLIPTA dry powder inhaler (DPI) via inhalation route for a period of 24 weeks. Participants were administered other prescribed COPD medications such as rescue medications according to usual practice, as suggested by physician.

| | |
|-----------------------|------------------|
| Reporting group title | Non-Ellipta MITT |
|-----------------------|------------------|

Reporting group description:

Eligible participants received the inhaled corticosteroid (ICS)/long-acting muscarinic receptor antagonist (LAMA)/long-acting beta agonist (LABA) products twice daily as prescribed by the physician for a period of 24 weeks. Participants were administered other prescribed COPD medications such as rescue medications according to usual practice, as suggested by physician.

| Serious adverse events | FF/UMEC/VI 100/62.5/25 | Non-Ellipta MITT | |
|---|---------------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 114 / 1545 (7.38%) | 114 / 1547 (7.37%) | |
| number of deaths (all causes) | 8 | 8 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 2 / 1547 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm malignant | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 1545 (0.06%) | 2 / 1547 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 2 / 1547 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal carcinoma | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small cell lung cancer | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast cancer metastatic | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hodgkin's disease | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung squamous cell carcinoma stage II | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mesothelioma | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Non-small cell lung cancer metastatic | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pituitary tumour benign | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural mesothelioma | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small cell lung cancer limited stage | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| T-cell lymphoma stage IV | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 2 / 1545 (0.13%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral ischaemia | | | |

| | | | |
|--|------------------|------------------|--|
| subjects affected / exposed | 1 / 1545 (0.06%) | 2 / 1547 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 2 / 1545 (0.13%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Iliac artery occlusion | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery occlusion | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (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 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| 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 | 0 / 1545 (0.00%) | 2 / 1547 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 0 / 1545 (0.00%) | 2 / 1547 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 26 / 1545 (1.68%) | 28 / 1547 (1.81%) | |
| occurrences causally related to treatment / all | 2 / 28 | 1 / 29 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 4 / 1547 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|------------------|--|
| Respiratory failure | | | |
| subjects affected / exposed | 3 / 1545 (0.19%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 2 / 1547 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 3 / 1545 (0.19%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 2 / 1547 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural | | | |

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| complications | | | |
| Fall | | | |
| subjects affected / exposed | 2 / 1545 (0.13%) | 3 / 1547 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 2 / 1545 (0.13%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ankle fracture | | | |
| subjects affected / exposed | 2 / 1545 (0.13%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 2 / 1547 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overdose | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |

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|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin laceration | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal fracture | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| 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 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 5 / 1545 (0.32%) | 5 / 1547 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Cardiac failure | | | |
| subjects affected / exposed | 3 / 1545 (0.19%) | 7 / 1547 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 4 / 1545 (0.26%) | 5 / 1547 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |

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|---|------------------|------------------|--|
| subjects affected / exposed | 5 / 1545 (0.32%) | 2 / 1547 (0.13%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina pectoris | | | |
| subjects affected / exposed | 2 / 1545 (0.13%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (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 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac asthma | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure chronic | | | |

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|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cor pulmonale | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular failure | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular hypokinesia | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain stem infarction | | | |

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| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral venous thrombosis | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peroneal nerve palsy | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reversible ischaemic neurological deficit | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sensory loss | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |

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| Vestibular disorder | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Diplopia | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diverticulum intestinal | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal polyp haemorrhage | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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| Incarcerated umbilical hernia subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (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 | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal haemorrhage subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders Cholecystitis subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (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 Renal failure subjects affected / exposed | 0 / 1545 (0.00%) | 2 / 1547 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

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| Bladder perforation | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (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 | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteolysis | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 26 / 1545 (1.68%) | 30 / 1547 (1.94%) | |
| occurrences causally related to treatment / all | 5 / 27 | 4 / 30 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |

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| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 6 / 1545 (0.39%) | 9 / 1547 (0.58%) | |
| occurrences causally related to treatment / all | 3 / 6 | 1 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 1545 (0.19%) | 2 / 1547 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 1545 (0.13%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Corynebacterium infection | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal viral infection | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemophilus infection | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Necrotising fasciitis | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia haemophilus | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia pneumococcal | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory syncytial virus bronchiolitis | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary bladder abscess | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Fluid retention | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 1545 (0.06%) | 0 / 1547 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock hypoglycaemic | | | |
| subjects affected / exposed | 0 / 1545 (0.00%) | 1 / 1547 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | FF/UMEC/VI 100/62.5/25 | Non-Ellipta MITT | |
|---|---------------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 32 / 1545 (2.07%) | 3 / 1547 (0.19%) | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 32 / 1545 (2.07%) | 3 / 1547 (0.19%) | |
| occurrences (all) | 32 | 3 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 15 February 2018 | Amendment 01: Addition of health Canada requirements for reporting of unusual failure in efficacy for new drugs to the marketed health products directorate in the section: additional adverse event reporting requirements for Canadian investigators; change to allow collection of both pre-and postbronchodilator spirometry at Visit 1 in the section: study assessment and procedures: lung function; collection of participant pulmonary rehabilitation programme details in the section: treatments: concomitant therapy; wording added to describe the reporting requirements for medical devices and defective inhalers in the section: safety assessments; consenting Visit 0 added the maximum time allowed between consent, screening and randomization was set to 6 weeks in schedule of activities; editing for clarity/ consistency and corrections of typographical errors throughout the document. |
| 28 September 2018 | Amendment 02: Addition of requirement to collect the most recent historical eosinophil count data in schedule of activities; changed source of safety information used by the investigator for Trelegy from the summary of participant characteristics to the investigator brochure in the section: risk mitigation; addition of requirement to collect the most recent historical eosinophil count data in the section: data collection; rationale for collection of historical eosinophil counts, whole blood count and % eosinophils was added; changed source of safety information used by the investigator for Trelegy from the summary of participant characteristics to the investigator brochure in the section: treatment of overdose; to provide clarity on the reporting requirements and what a drug/device combination is in the section: GSK medical device GSK drug/device combinations incidents; changed source of safety information used by the investigator for Trelegy from the summary of participant characteristics to the investigator brochure in the section: medications; addition of references to provide background to eosinophil data collection in the section: references. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported