# Clinical trial results:
# A Phase III, Randomized, Observer-Blind, Controlled, Multicenter Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of an MF59-Adjuvanted Quadrivalent Influenza Vaccine Compared to Non-influenza Vaccine Comparator in Adults  65 Years of Age

## Summary

| | |
|---|---|
| EudraCT number | 2015-000728-27 |
| Trial protocol | EE PL LV CZ LT RO BG |
| Global end of trial date | 05 September 2018 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 22 September 2019 |
| First version publication date | 22 September 2019 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | V118_18 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02587221 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Seqirus UK Limited |
| Sponsor organisation address | The Point, 29 Market Street, Maidenhead, United Kingdom, SL6 8AA |
| Public contact | Clinical Trial Disclosure Manager,  Seqirus UK Limited , Seqirus.Clinicaltrials@seqirus.com |
| Scientific contact | Clinical Trial Disclosure Manager,  Seqirus UK Limited , Seqirus.Clinicaltrials@seqirus.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 | 23 July 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 23 July 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 September 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Primary efficacy objective: To demonstrate absolute vaccine efficacy of aQIV versus non-influenza comparator (Boostrix®) when administered as a single dose to prevent first occurrence RT-PCR-confirmed influenza, due to any strain of influenza regardless of antigenic match to the strains selected for the seasonal vaccine, in subjects ≥ 65 years of age.

Primary safety objectives: To evaluate the safety of aQIV through assessment for local and systemic solicited adverse events through Day 7 in a subset of subjects.
- To evaluate the rates in each vaccine group of medically-attended adverse events within 30 days after the first occurrence RT-PCR confirmed ILI.
- To evaluate the rates in each vaccine group of unsolicited adverse events for 21 days after vaccination and adverse events leading to withdrawal, serious adverse events (SAEs), adverse events of special interest (AESI), and new onset of chronic diseases (NOCD) for 365 days after vaccination.

Protection of trial subjects:

This clinical study was designed and was implemented and reported in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations including European Directive 2001/20/EC, US Code of Federal Regulations (CFR) Title 21, and Japanese Ministry of Health, Labor, and Welfare, sponsor codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki European Council 2001, US CFR, ICH 1997).

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 30 September 2016 |
| 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 | Bulgaria: 366 |
| Country: Number of subjects enrolled | Colombia: 1224 |
| Country: Number of subjects enrolled | Czech Republic: 366 |
| Country: Number of subjects enrolled | Estonia: 641 |
| Country: Number of subjects enrolled | Latvia: 282 |
| Country: Number of subjects enrolled | Lithuania: 447 |
| Country: Number of subjects enrolled | Malaysia: 899 |
| Country: Number of subjects enrolled | Philippines: 910 |
| Country: Number of subjects enrolled | Poland: 719 |
| Country: Number of subjects enrolled | Romania: 356 |

| | |
|---|---|
| Country: Number of subjects enrolled | Thailand: 490 |
| Country: Number of subjects enrolled | Turkey: 90 |
| Worldwide total number of subjects | 6790 |
| EEA total number of subjects | 3177 |

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) | 0 |
| From 65 to 84 years | 6643 |
| 85 years and over | 147 |

## Subject disposition

### Recruitment

Recruitment details:

The study enrolled male and female adults ≥ 65 years old who were healthy or had co-morbidities.

### Pre-assignment

Screening details:

Screening criteria applied.

### Period 1

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

Blinding implementation details:

The study was observer blind.

### Arms

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

Arm description:

A single dose of approximately 0.5 mL of aQIV was administered on Day 1.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | MF59-adjuvanted Quadrivalent Subunit Inactivated Egg-derived Influenza Vaccine (aQIV) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

1 dose approximately 0.5 mL of aQIV

| | |
|---|---|
| **Arm title** | Non-influenza Comparator Vaccine |

Arm description:

1 dose approximately 0.5 mL dose of Non-influenza comparator vaccine (Boostrix)

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed |
| Investigational medicinal product code | |
| Other name | Boostrix |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

1 dose approximately 0.5 mL dose of Non-influenza comparator vaccine (Boostrix)

| **Number of subjects in period 1** | aQIV | Non-influenza Comparator Vaccine |
|---|---|---|
| Started | 3394 | 3396 |
| Treated | 3379 | 3382 |
| Completed | 3263 | 3273 |
| Not completed | 131 | 123 |
| Adverse event, serious fatal | 33 | 34 |
| Consent withdrawn by subject | 66 | 61 |
| Other Reason or Unspecified | 2 | 1 |
| Adverse event, non-fatal | 3 | 3 |
| Lost to follow-up | 21 | 19 |
| Protocol deviation | 6 | 5 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | aQIV |
| Reporting group description: | |
| A single dose of approximately 0.5 mL of aQIV was administered on Day 1. | |
| Reporting group title | Non-influenza Comparator Vaccine |
| Reporting group description: | |
| 1 dose approximately 0.5 mL dose of Non-influenza comparator vaccine (Boostrix) | |

| Reporting group values | aQIV | Non-influenza Comparator Vaccine | Total |
|---|---|---|---|
| Number of subjects | 3394 | 3396 | 6790 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 3309 | 3334 | 6643 |
| 85 years and over | 85 | 62 | 147 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 71.9 | 71.8 | |
| standard deviation | ± 5.53 | ± 5.36 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 2105 | 2089 | 4194 |
| Male | 1289 | 1307 | 2596 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 615 | 607 | 1222 |
| Not Hispanic or Latino | 2773 | 2779 | 5552 |
| Unknown or Not Reported | 6 | 10 | 16 |
| Race/Ethnicity<br>Units: Subjects | | | |
| American Indian or Alaska Native | 62 | 59 | 121 |
| Asian | 1139 | 1159 | 2298 |
| Black or African American | 1 | 0 | 1 |
| White | 1642 | 1629 | 3271 |
| Other | 550 | 549 | 1099 |
| Previous Seasonal Influenza Vaccine in the Past 5 Years<br>Units: Subjects | | | |
| Yes | 991 | 1021 | 2012 |

| | | | |
|---|---|---|---|
| No | 2403 | 2375 | 4778 |
| Comorbidity Score | | | |
| Comorbidity risk scores were assessed among other baseline characteristics as a validated predictor of risk of influenza complications in subjects ≥65 years of age using a model-based approach assessing 5 disease classifications (pulmonary disease, heart disease, renal disease, dementia or stroke, and non-hematological and hematological cancer [excluding cancer of the skin other than melanoma]). Using this model, a score of <50 was considered low risk and a score of ≥50 was considered high risk for hospitalization due to pneumonia or influenza and death from any cause. | | | |
| Units: Subjects | | | |
| < 50 | 2472 | 2474 | 4946 |
| ≥ 50 | 922 | 922 | 1844 |
| Smoking Status<br>Units: Subjects | | | |
| Smoking | 325 | 335 | 660 |
| Not smoking | 3069 | 3061 | 6130 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | aQIV |
| Reporting group description: | |
| A single dose of approximately 0.5 mL of aQIV was administered on Day 1. | |
| Reporting group title | Non-influenza Comparator Vaccine |
| Reporting group description: | |
| 1 dose approximately 0.5 mL dose of Non-influenza comparator vaccine (Boostrix) | |
| Subject analysis set title | VE (aQIV vs Boostrix) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| aQIV: A single dose of approximately 0.5 mL of aQIV was administered on Day 1 (NH 2016/17, SH 2017).<br>Non-influenza Comparator Vaccine: A single dose of approximately 0.5 mL dose of Boostrix was administered on Day 1 (NH 2016/17, SH 2017).<br>aQIV N=3368 ; Boostrix N=3372. | |

### Primary: Efficacy Endpoint: First-occurrence of RT-PCR-Confirmed Influenza Due to Any Strain of Influenza Regardless of Antigenic Match to the Strains Selected for the Seasonal Vaccine Occurring ≥21 Days After Vaccination

| | |
|---|---|
| End point title | Efficacy Endpoint: First-occurrence of RT-PCR-Confirmed Influenza Due to Any Strain of Influenza Regardless of Antigenic Match to the Strains Selected for the Seasonal Vaccine Occurring ≥21 Days After Vaccination |
| End point description: | |
| First occurrence of event: Number of subjects with reverse transcription polymerase chain reaction (RT-PCR)-confirmed influenza due to any strain regardless of antigenic match to the strains selected for the seasonal vaccine was determined for aQIV vs the non-influenza comparator (Boostrix®) in subjects ≥65 years of age. An influenza like illness (ILI) was defined as presence of ≥1 respiratory symptom (sore throat, cough, sputum production, wheezing, or difficulty breathing) concurrently with ≥1 systemic symptom (temp >37.2°C/99°F, chills, tiredness, headache, or myalgia). The Full Analysis Set (FAS) Efficacy, consisting of all randomized subjects who received a study treatment, were under observation for at least 21 days post-vaccination, and provided efficacy data, was used for analysis. | |
| End point type | Primary |
| End point timeframe: | |
| Day 21 to Day 180 after vaccination or end of influenza season, whichever is longer | |

| End point values | aQIV | Non-influenza Comparator Vaccine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3368 | 3372 | | |
| Units: subjects | 122 | 151 | | |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | VE (aQIV vs Boostrix) |
| Statistical analysis description: | |
| Vaccine Efficacy (VE)=(1-Hazard Ratio of aQIV vs Boostrix)*100%. Success criteria: LL of the two-sided | |

97.45% CI of Vaccine Efficacy exceeds 40% after considering alpha used in interim analysis using the protocol ILI definition. Result is based on the Cox Proportional Hazards model for time until onset of the first RT-PCR confirmed influenza with vaccine group as the main effect, adjusting for age group, study site and comorbidity as random effects calculated using Maximum Likelihood (ML) method

| | |
|---|---|
| Comparison groups | aQIV v Non-influenza Comparator Vaccine |
| Number of subjects included in analysis | 6740 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Vaccine efficacy |
| Point estimate | 19.8 |
| Confidence interval | |
| level | Other: 97.45 % |
| sides | 2-sided |
| lower limit | -5.27 |
| upper limit | 38.91 |

## Primary: Safety Endpoint: The Percentage of Subjects in the Solicited Safety Subset With Solicited Local and Systemic Adverse Events (AE)

| | |
|---|---|
| End point title | Safety Endpoint: The Percentage of Subjects in the Solicited Safety Subset With Solicited Local and Systemic Adverse Events (AE)[1] |

End point description:

Safety of vaccination was assessed in terms of percentage of subjects reporting solicited local and systemic AEs up to 7 days after vaccination. The Solicited Safety Set, consisting of a randomly selected subset of all treated subjects, with solicited safety assessments beyond 30 minutes, was used for analysis.

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

End point timeframe:

Day 1 through Day 7

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analyses for this endpoint were performed with descriptive statistics

| **End point values** | aQIV | Non-influenza Comparator Vaccine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 665 | 667 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Any solicited AE | 34.3 | 32.2 | | |
| Any local solicited AE | 24.4 | 19.6 | | |
| Any systemic solicited AE | 19.2 | 16.3 | | |
| Other | 6.2 | 3.9 | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Safety Endpoint: Percentage of Subjects With Medically-attended Adverse Events

| End point title | Safety Endpoint: Percentage of Subjects With Medically-attended Adverse Events[2] |
|---|---|

End point description:

Safety of vaccination was assessed in terms of percentage of subjects reporting medically attended AEs within 30 days after of first occurrence RT-PCR confirmed influenza. The FAS Efficacy, consisting of all randomized subjects who received a study treatment, were under observation for at least 21 days post-vaccination, and provided efficacy data, was used for analysis.

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

End point timeframe:

Within 30 days after of first occurrence RT-PCR confirmed Influenza

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analyses for this endpoint were performed with descriptive statistics.

| **End point values** | aQIV | Non-influenza Comparator Vaccine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3368 | 3372 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 0.7 | 0.4 | | |

### Statistical analyses

No statistical analyses for this end point

## Primary: Safety Endpoint: Percentages of Subjects With Any Unsolicited AE

| End point title | Safety Endpoint: Percentages of Subjects With Any Unsolicited AE[3] |
|---|---|

End point description:

Safety of vaccination was assessed in terms of percentage of subjects reporting unsolicited AEs up to 21 days after vaccination. The Unsolicited Safety Set consisting of treated subjects with unsolicited AE data was used for analysis.

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

End point timeframe:

Day 1 through Day 366

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analyses for this endpoint were performed with descriptive statistics.

| **End point values** | aQIV | Non-influenza Comparator Vaccine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3380 | 3377 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 21.5 | 21.2 | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Safety Endpoint: Percentages of Subjects With Serious Adverse Events (SAE), AEs Leading to Withdrawal, New Onset of Chronic Disease (NOCD), and Adverse Events of Special Interest (AESI)

| End point title | Safety Endpoint: Percentages of Subjects With Serious Adverse Events (SAE), AEs Leading to Withdrawal, New Onset of Chronic Disease (NOCD), and Adverse Events of Special Interest (AESI)[4] |
|---|---|

End point description:

Safety of vaccination was assessed in terms of percentage of subjects reporting SAEs, AEs leading to withdrawal, NOCDs, and AESIs up to 366 days after vaccination. The Unsolicited Safety Set consisting of treated subjects with unsolicited AE data was used for analysis.

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

End point timeframe:

Day 1 to Day 366

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analyses for this endpoint were performed with descriptive statistics.

| **End point values** | aQIV | Non-influenza Comparator Vaccine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3380 | 3377 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Any unsolicited SAE | 7.0 | 6.9 | | |
| Any related SAE | 0.0 | 0.0 | | |
| Any unsolicited AEs leading to withdrawal | 1.1 | 1.1 | | |
| Any NOCD | 9.5 | 9.0 | | |
| Any AESI | 0.1 | 0.2 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Efficacy Endpoint: First-occurrence RT-PCR-confirmed Influenza Due to Any Strain of Influenza Regardless of Antigenic Match to the Strains Selected for the Seasonal Vaccine (Modified CDC and WHO Definitions) Occurring ≥21 Days After Vaccination

| End point title | Efficacy Endpoint: First-occurrence RT-PCR-confirmed Influenza Due to Any Strain of Influenza Regardless of Antigenic Match to |
|---|---|

| | |
|---|---|
| | the Strains Selected for the Seasonal Vaccine (Modified CDC and WHO Definitions) Occurring ≥21 Days After Vaccination |

End point description:

First occurrence of event: Number of subjects with RT-PCR-confirmed influenza due to any strain regardless of antigenic match to strains selected for the seasonal vaccine was determined for aQIV and Boostrix in subjects ≥65 years of age. Two definitions of ILI were used: modified CDC ILI definition defined as presence of fever (temperature >37.2°C) with cough or sore throat and the WHO ILI definition consisting of fever (temperature ≥38.0°C) with cough. The WHO ILI definition was used in a post-hoc analysis. The FAS Efficacy, consisting of all randomized subjects who received a study treatment, were under observation for at least 21 days post-vaccination, and provided efficacy data, was used for analysis.

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

End point timeframe:

Day 21 to Day 180 after vaccination or end of influenza season, whichever is longer

| **End point values** | aQIV | Non-influenza Comparator Vaccine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3368 | 3372 | | |
| Units: Subjects | | | | |
| Modified CDC definition | 83 | 121 | | |
| WHO definition | 39 | 79 | | |

## Statistical analyses

| **Statistical analysis title** | VE (aQIV vs Boostrix) for Modified CDC ILI |
|---|---|

Statistical analysis description:

VE=(1-Hazard Ratio of aQIV vs Boostrix)*100%. Result is based on the Cox Proportional Hazards model for time until onset of the first RT-PCR confirmed influenza with vaccine group as the main effect, adjusting for age group, study site and comorbidity as random effects calculated using the ML method.

| | |
|---|---|
| Comparison groups | aQIV v Non-influenza Comparator Vaccine |
| Number of subjects included in analysis | 6740 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Vaccine efficacy |
| Point estimate | 32.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 10.23 |
| upper limit | 48.67 |

| **Statistical analysis title** | VE (aQIV vs Boostrix) for WHO ILI |
|---|---|

Statistical analysis description:

VE=(1-Hazard Ratio of aQIV vs Boostrix)*100%. Result is based on the Cox Proportional Hazards model for time until onset of the first RT-PCR confirmed influenza with vaccine group as the main effect, adjusting for age group, study site and comorbidity as random effects calculated using the ML method.

| | |
|---|---|
| Comparison groups | Non-influenza Comparator Vaccine v aQIV |
| Number of subjects included in analysis | 6740 |
| Analysis specification | Post-hoc |
| Analysis type | other |
| Parameter estimate | Vaccine efficacy |
| Point estimate | 51.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 28.21 |
| upper limit | 66.67 |

## Secondary: Efficacy Endpoint: First-occurrence Culture-confirmed Influenza Due to Any Strain of Influenza Antigenically Matched to the Strains Selected for the Seasonal Vaccine Occurring ≥21 Days After Vaccination

| | |
|---|---|
| End point title | Efficacy Endpoint: First-occurrence Culture-confirmed Influenza Due to Any Strain of Influenza Antigenically Matched to the Strains Selected for the Seasonal Vaccine Occurring ≥21 Days After Vaccination |

End point description:

First occurrence of event: Number of subjects with culture-confirmed influenza due to any strain antigenically matched to the strains selected for the seasonal vaccine was determined for aQIV and Boostrix in subjects ≥ 65 years of age. An ILI was defined as presence of at least one respiratory symptom (sore throat, cough, sputum production, wheezing, or difficulty breathing) concurrently with at least one systemic symptom (temperature >37.2°C/99°F, chills, tiredness, headache, or myalgia). Two additional definitions of ILI were used: modified CDC ILI definition defined as presence of fever (temperature >37.2°C) with cough or sore throat and the WHO ILI definition consisting of fever (temperature ≥38.0°C) with cough. The WHO ILI definition was used in a post-hoc analysis. The FAS Efficacy was used for analysis.

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

End point timeframe:

Day 21 to Day 180 after vaccination or end of influenza season, whichever is longer

| **End point values** | aQIV | Non-influenza Comparator Vaccine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3368 | 3372 | | |
| Units: subjects | | | | |
| Protocol definition | 7 | 14 | | |
| Modified CDC definition | 5 | 13 | | |
| WHO definition | 2 | 8 | | |

## Statistical analyses

| **Statistical analysis title** | VE (aQIV vs Boostrix) for Protocol-defined IL |
|---|---|

Statistical analysis description:

VE=(1-Hazard Ratio of aQIV vs Boostrix)*100%. Result is based on the Cox Proportional Hazards model

for time until onset of the first culture confirmed influenza with vaccine group as the main effect, adjusting for age group, study site and comorbidity as random effects calculated using the ML method.

| | |
|---|---|
| Comparison groups | Non-influenza Comparator Vaccine v aQIV |
| Number of subjects included in analysis | 6740 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Vaccine efficacy |
| Point estimate | 49.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -24.03 |
| upper limit | 79.79 |

| **Statistical analysis title** | VE (aQIV vs Boostrix) for Modified CDC ILI |
|---|---|

Statistical analysis description:

VE=(1-Hazard Ratio of aQIV vs Boostrix)*100%. Result is based on the Cox Proportional Hazards model for time until onset of the first culture confirmed influenza with vaccine group as the main effect, adjusting for age group, study site and comorbidity as random effects calculated using the ML method.

| | |
|---|---|
| Comparison groups | Non-influenza Comparator Vaccine v aQIV |
| Number of subjects included in analysis | 6740 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Vaccine efficacy |
| Point estimate | 61.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.98 |
| upper limit | 86.28 |

| **Statistical analysis title** | VE (aQIV vs Boostrix) for WHO ILI |
|---|---|

Statistical analysis description:

VE=(1-Hazard Ratio of aQIV vs Boostrix)*100%. Result is based on the Cox Proportional Hazards model for time until onset of the first culture confirmed influenza with vaccine group as the main effect, adjusting for age group, study site and comorbidity as random effects calculated using the ML method.

| | |
|---|---|
| Comparison groups | Non-influenza Comparator Vaccine v aQIV |
| Number of subjects included in analysis | 6740 |
| Analysis specification | Post-hoc |
| Analysis type | other |
| Parameter estimate | Vaccine efficacy |
| Point estimate | 74.96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.93 |
| upper limit | 94.68 |

## Secondary: Efficacy Endpoint: First-occurrence Culture-confirmed Influenza Due to Any Strain of Influenza Regardless of Antigenic Match to the Strains Selected for the Seasonal Vaccine Occurring ≥21 Days After Vaccination

| | |
|---|---|
| End point title | Efficacy Endpoint: First-occurrence Culture-confirmed Influenza Due to Any Strain of Influenza Regardless of Antigenic Match to the Strains Selected for the Seasonal Vaccine Occurring ≥21 Days After Vaccination |

End point description:

First occurrence of event: Number of subjects with culture-confirmed influenza due to any strain regardless of antigenic match to the strains selected for the seasonal vaccine was determined for aQIV and Boostrix in subjects ≥65 years of age. An ILI was defined as presence of at least one respiratory symptom (sore throat, cough, sputum production, wheezing, or difficulty breathing) concurrently with at least one systemic symptom (temperature >37.2°C/99°F, chills, tiredness, headache, or myalgia). Two additional definitions of ILI were used: modified CDC ILI definition defined as presence of fever (temperature >37.2°C) with cough or sore throat and the WHO ILI definition consisting of fever (temperature ≥38.0°C) with cough. The WHO ILI definition was used in a post-hoc analysis. The FAS Efficacy was used for analysis.

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

End point timeframe:

Day 21 to Day 180 after vaccination or end of influenza season, whichever is longer

| **End point values** | aQIV | Non-influenza Comparator Vaccine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3368 | 3372 | | |
| Units: subjects | | | | |
| Protocol definition | 58 | 81 | | |
| Modified CDC definition | 44 | 66 | | |
| WHO definition | 18 | 45 | | |

### Statistical analyses

| **Statistical analysis title** | VE (aQIV vs Boostrix) for Protocol-defined IL |
|---|---|

Statistical analysis description:

VE=(1-Hazard Ratio of aQIV vs Boostrix)*100%. Result is based on the Cox Proportional Hazards model for time until onset of the first culture confirmed influenza with vaccine group as the main effect, adjusting for age group, study site and comorbidity as random effects calculated using the ML method.

| | |
|---|---|
| Comparison groups | Non-influenza Comparator Vaccine v aQIV |
| Number of subjects included in analysis | 6740 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Vaccine efficacy |
| Point estimate | 28.66 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.05 |
| upper limit | 49.08 |

| **Statistical analysis title** | VE (aQIV vs Boostrix) for Modified CDC ILI |
|---|---|

Statistical analysis description:

VE=(1-Hazard Ratio of aQIV vs Boostrix)*100%. Result is based on the Cox Proportional Hazards model for time until onset of the first culture confirmed influenza with vaccine group as the main effect, adjusting for age group, study site and comorbidity as random effects calculated using the ML method.

| | |
|---|---|
| Comparison groups | Non-influenza Comparator Vaccine v aQIV |
| Number of subjects included in analysis | 6740 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Vaccine efficacy |
| Point estimate | 33.47 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.56 |
| upper limit | 54.57 |

| **Statistical analysis title** | VE (aQIV vs Boostrix) for WHO ILI |
|---|---|

Statistical analysis description:

VE=(1-Hazard Ratio of aQIV vs Boostrix)*100%. Result is based on the Cox Proportional Hazards model for time until onset of the first culture confirmed influenza with vaccine group as the main effect, adjusting for age group, study site and comorbidity as random effects calculated using the ML method.

| | |
|---|---|
| Comparison groups | Non-influenza Comparator Vaccine v aQIV |
| Number of subjects included in analysis | 6740 |
| Analysis specification | Post-hoc |
| Analysis type | other |
| Parameter estimate | Vaccine efficacy |
| Point estimate | 60.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 31.19 |
| upper limit | 76.94 |

## Secondary: Efficacy Endpoint: First-occurrence Culture-confirmed Influenza Due to Any Strain of Influenza Antigenically Unmatched to the Strains Selected for the Seasonal Vaccine Occurring ≥21 Days After Vaccination

| | |
|---|---|
| End point title | Efficacy Endpoint: First-occurrence Culture-confirmed Influenza Due to Any Strain of Influenza Antigenically Unmatched to the Strains Selected for the Seasonal Vaccine Occurring ≥21 Days |

| | |
|---|---|
| | After Vaccination |

End point description:

First occurrence of event: Number of subjects with culture-confirmed influenza due to any strain antigenically unmatched to the strains selected for the seasonal vaccine was determined for aQIV and Boostrix in subjects ≥ 65 years of age. An ILI was defined as presence of at least one respiratory symptom (sore throat, cough, sputum production, wheezing, or difficulty breathing) concurrently with at least one systemic symptom (temperature >37.2°C/99°F, chills, tiredness, headache, or myalgia). Two additional definitions of ILI were used: modified CDC ILI definition defined as presence of fever (temperature >37.2°C) with cough or sore throat and the WHO ILI definition consisting of fever (temperature ≥38.0°C) with cough. The WHO ILI definition was used in a post-hoc analysis. The FAS Efficacy was used for analysis.

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

End point timeframe:

Day 21 to Day 180 after vaccination or end of influenza season, whichever is longer

| **End point values** | aQIV | Non-influenza Comparator Vaccine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3368 | 3372 | | |
| Units: subjects | | | | |
| Protocol definition | 51 | 67 | | |
| Modified CDC definition | 39 | 53 | | |
| WHO definition | 16 | 37 | | |

## Statistical analyses

| **Statistical analysis title** | VE (aQIV vs Boostrix) for Protocol-defined ILI |
|---|---|

Statistical analysis description:

VE=(1-Hazard Ratio of aQIV vs Boostrix)*100%. Result is based on the Cox Proportional Hazards model for time until onset of the first culture confirmed influenza with vaccine group as the main effect, adjusting for age group, study site and comorbidity as random effects calculated using the ML method.

| | |
|---|---|
| Comparison groups | Non-influenza Comparator Vaccine v aQIV |
| Number of subjects included in analysis | 6740 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Vaccine efficacy |
| Point estimate | 23.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.69 |
| upper limit | 47.05 |

| **Statistical analysis title** | VE (aQIV vs Boostrix) for Modified CDC ILI |
|---|---|

Statistical analysis description:

VE=(1-Hazard Ratio of aQIV vs Boostrix)*100%. Result is based on the Cox Proportional Hazards model

for time until onset of the first culture confirmed influenza with vaccine group as the main effect, adjusting for age group, study site and comorbidity as random effects calculated using the ML method.

| | |
|---|---|
| Comparison groups | aQIV v Non-influenza Comparator Vaccine |
| Number of subjects included in analysis | 6740 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Vaccine efficacy |
| Point estimate | 26.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.71 |
| upper limit | 51.13 |

| | |
|---|---|
| **Statistical analysis title** | VE (aQIV vs Boostrix) for WHO ILI |

Statistical analysis description:

VE=(1-Hazard Ratio of aQIV vs Boostrix)*100%. Result is based on the Cox Proportional Hazards model for time until onset of the first culture confirmed influenza with vaccine group as the main effect, adjusting for age group, study site and comorbidity as random effects calculated using the ML method.

| | |
|---|---|
| Comparison groups | aQIV v Non-influenza Comparator Vaccine |
| Number of subjects included in analysis | 6740 |
| Analysis specification | Post-hoc |
| Analysis type | other |
| Parameter estimate | Vaccine efficacy |
| Point estimate | 57.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 22.73 |
| upper limit | 76.09 |

## Secondary: Efficacy Endpoint: First-occurrence RT-PCR-confirmed Influenza Due to Any Strain of Influenza Regardless of Antigenic Match to the Strains Selected for the Seasonal Vaccine Occurring ≥7 Days After Vaccination

| | |
|---|---|
| End point title | Efficacy Endpoint: First-occurrence RT-PCR-confirmed Influenza Due to Any Strain of Influenza Regardless of Antigenic Match to the Strains Selected for the Seasonal Vaccine Occurring ≥7 Days After Vaccination |

End point description:

First occurrence of event: Number of subjects with culture-confirmed influenza due to any strain regardless of antigenic match to the strains selected for the seasonal vaccine was determined for aQIV and Boostrix in subjects ≥ 65 years of age. An ILI was defined as presence of at least one respiratory symptom (sore throat, cough, sputum production, wheezing, or difficulty breathing) concurrently with at least one systemic symptom (temperature >37.2°C/99°F, chills, tiredness, headache, or myalgia). An additional definition of ILI was also used: modified CDC ILI definition defined as presence of fever (temperature >37.2°C) with cough or sore throat. The FAS Early Efficacy consisting of all randomized subjects who received a study treatment and were under observation from 7 to 180 days after treatment was used for analysis.

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

End point timeframe:

Day 7 to Day 180 after vaccination or end of influenza season, whichever is longer

| **End point values** | aQIV | Non-influenza Comparator Vaccine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3376 | 3376 | | |
| Units: subjects | | | | |
| Protocol definition | 140 | 163 | | |
| Modified CDC definition | 97 | 130 | | |

## Statistical analyses

| **Statistical analysis title** | VE (aQIV vs Boostrix) for Protocol-defined ILI |
|---|---|

Statistical analysis description:

Vaccine Efficacy=hazard ratio of aQIV vs Boostrix. Result is based on the Cox Proportional Hazards model for time until onset of the first RT-PCR confirmed influenza with vaccine group as the main effect, adjusting for age group, study site and comorbidity as random effects calculated using the ML method.

| | |
|---|---|
| Comparison groups | aQIV v Non-influenza Comparator Vaccine |
| Number of subjects included in analysis | 6752 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Vaccine efficacy |
| Point estimate | 14.44 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.25 |
| upper limit | 31.74 |

| **Statistical analysis title** | VE (aQIV vs Boostrix) for Modified CDC ILI |
|---|---|

Statistical analysis description:

VE=(1-Hazard Ratio of aQIV vs Boostrix)*100%. Result is based on the Cox Proportional Hazards model for time until onset of the first RT-PCR confirmed influenza with vaccine group as the main effect, adjusting for age group, study site and comorbidity as random effects calculated using the ML method.

| | |
|---|---|
| Comparison groups | aQIV v Non-influenza Comparator Vaccine |
| Number of subjects included in analysis | 6752 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Vaccine efficacy |
| Point estimate | 25.93 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.64 |
| upper limit | 43.06 |

## Secondary: Immunogenicity Endpoint: Geometric Mean Hemagglutination Inhibition (HI) Titers (GMT)

| End point title | Immunogenicity Endpoint: Geometric Mean Hemagglutination Inhibition (HI) Titers (GMT)[5] |
|---|---|

End point description:

The log-transformed antibody titers (GMT) at Day 1 and Day 22 were evaluated using an analysis of covariance (ANCOVA) model including factors for site/country, pre-vaccination titer, age, and comorbidity. The FAS Immunogenicity, consisting of all randomized subjects who received a study treatment, and provided immunogenicity data at Days 1 and 22, was used for analysis.

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

End point timeframe:

Days 1 and 22

Notes:

[5] - 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: Inter-group statistical comparison was not performed.

| **End point values** | aQIV | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1324 | | | |
| Units: geometric mean titer | | | | |
| geometric mean (confidence interval 95%) | | | | |
| A/H1N1 Day 1 | 31.86 (28.49 to 35.63) | | | |
| A/H1N1 Day 22 | 438.79 (403.82 to 476.79) | | | |
| A/H3N2 Day 1 | 28.31 (25.43 to 31.52) | | | |
| A/H3N2 Day 22 | 572.80 (525.08 to 624.86) | | | |
| B/Yamagata Day 1 | 13.83 (12.81 to 14.92) | | | |
| B/Yamagata Day 22 | 86.77 (79.94 to 94.19) | | | |
| B/Victoria Day 1 | 12.77 (11.81 to 13.81) | | | |
| B/Victoria Day 22 | 104.26 (95.77 to 113.50) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Immunogenicity Endpoint: Geometric Mean Ratio (GMR) of Post-vaccination HI Titer Over the Pre-vaccination HI Titer

| End point title | Immunogenicity Endpoint: Geometric Mean Ratio (GMR) of Post-vaccination HI Titer Over the Pre-vaccination HI Titer[6] |
|---|---|

End point description:

The GMR was assessed as the postvaccination HI titer divided by the prevaccination HI titer (Day 22/Day 1). The FAS Immunogenicity, consisting of all randomized subjects who received a study treatment, and provided immunogenicity data at Days 1 and 22, was used for analysis.

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

End point timeframe:

Day 22/Day 1

Notes:

[6] - 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: Inter-group statistical comparison was not performed.

| End point values | aQIV | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1324 | | | |
| Units: geometric mean ratio | | | | |
| geometric mean (confidence interval 95%) | | | | |
| A/H1N1 | 14.17 (12.84 to 15.64) | | | |
| A/H3N2 | 22.65 (20.48 to 25.06) | | | |
| B/Yamagata | 6.58 (6.02 to 7.20) | | | |
| B/Victoria | 8.59 (7.83 to 9.42) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Immunogenicity Endpoint: Percentages of Subjects With an HI Titer ≥1:40

| End point title | Immunogenicity Endpoint: Percentages of Subjects With an HI Titer ≥1:40[7] |
|---|---|

End point description:

The percentage of subjects vaccinated with aQIV with a HI antibody titers ≥1:40 was assessed for each of the 4 strains. Assessment criteria was considered fulfilled if the lower bound of the two-sided 95% CI for percent of subjects with HI antibody titer ≥1:40 met or exceeded 60% at Day 22.
The FAS Immunogenicity consisting of all randomized subjects who received a study treatment, and provided immunogenicity data at Days 1 and 22 was used for analysis.

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

End point timeframe:

Day 22

Notes:

[7] - 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: Inter-group statistical comparison was not performed.

| **End point values** | aQIV | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1324 | | | |
| Units: percentage of subjects | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| A/H1N1 | 96.2 (95.05 to 97.18) | | | |
| A/H3N2 | 95.6 (94.37 to 96.66) | | | |
| B/Yamagata | 79.2 (76.95 to 81.40) | | | |
| B/Victoria | 81.6 (79.39 to 83.65) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Immunogenicity Endpoint: Percentages of Subjects Who Achieved Seroconversion (SCR)

| End point title | Immunogenicity Endpoint: Percentages of Subjects Who Achieved Seroconversion (SCR)[8] |
|---|---|

End point description:

The percentage of subjects achieving SCR at Day 22 was assessed for each of the 4 strains. SCR is defined as HI titer ≥1:40 for subjects seronegative at baseline (HI titer <1:10) or a minimum 4-fold increase in HI titer for subjects seropositive at baseline (HI titer ≥1:10) on Day 22. Assessment criteria was considered fulfilled if the lower bound of the two-sided 95% CI for the percentage of subjects achieving an HI antibody SCR met or exceeded 30% at Day 22. The FAS Immunogenicity consisting of all randomized subjects who received a study treatment, and provided immunogenicity data at Days 1 and 22 was used for analysis.

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

End point timeframe:

Day 22

Notes:

[8] - 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: Inter-group statistical comparison was not performed.

| **End point values** | aQIV | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1324 | | | |
| Units: percentage of subjects | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| A/H1N1 | 78.0 (75.66 to 80.21) | | | |

| | | | | |
|---|---|---|---|---|
| A/H3N2 | 84.6 (82.52 to 86.49) | | | |
| B/Yamagata | 60.8 (58.06 to 63.41) | | | |
| B/Victoria | 65.5 (62.88 to 68.10) | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: Solicited AEs: Day 1 to Day 7; SAEs: Day 1 to Day 366; and Unsolicited AEs: Day 1 to Day 22. | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.0 |

| Reporting groups | |
|---|---|
| Reporting group title | aQIV |
| Reporting group description: A single dose of approximately 0.5 mL of aQIV was administered on Day 1. | |
| Reporting group title | Non-influenza Comparator Vaccine |
| Reporting group description: 1 dose approximately 0.5 mL dose of Non-influenza comparator vaccine (Boostrix) | |

| Serious adverse events | aQIV | Non-influenza Comparator Vaccine | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 238 / 3380 (7.04%) | 234 / 3377 (6.93%) | |
| number of deaths (all causes) | 33 | 34 | |
| number of deaths resulting from adverse events | 1 | 2 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Prostate cancer | | | |
| subjects affected / exposed | 2 / 3380 (0.06%) | 3 / 3377 (0.09%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Plasma cell myeloma | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder neoplasm | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone neoplasm | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain neoplasm malignant | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer metastatic | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diffuse large B-cell lymphoma | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gallbladder adenoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gallbladder cancer | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head and neck cancer | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic cancer | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Intraductal proliferative breast lesion | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Invasive lobular breast carcinoma | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Lung adenocarcinoma stage IV | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphoma | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to liver | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic renal cell carcinoma | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Oesophageal adenocarcinoma | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian cancer | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic carcinoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Papillary thyroid cancer | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Penile cancer | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Polycythaemia vera | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal adenocarcinoma | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cancer metastatic | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Squamous cell carcinoma of lung | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thyroid cancer | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic neoplasm | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 7 / 3380 (0.21%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 2 / 3380 (0.06%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 3 / 3377 (0.09%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic stenosis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive emergency | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3380 (0.00%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic arteriosclerosis | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic dilatation | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic vascular disorder | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Essential hypertension | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery stenosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery thrombosis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 7 / 3380 (0.21%) | 3 / 3377 (0.09%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 7 | 0 / 3 | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Medical device pain | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| **Reproductive system and breast disorders** | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 3 / 3380 (0.09%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostatitis | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine prolapse | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterovaginal prolapse | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (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 | 12 / 3380 (0.36%) | 14 / 3377 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 3 / 3380 (0.09%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 4 / 3380 (0.12%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Bronchiectasis | | | |
| subjects affected / exposed | 2 / 3380 (0.06%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthma | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis chronic | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic respiratory failure | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (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 | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary infarction | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Restrictive pulmonary disease | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Sleep apnoea syndrome | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 2 / 3380 (0.06%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delusional disorder, unspecified type | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| 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 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Carbohydrate antigen 19-9 increased | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| 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 | | | |
| Femur fracture | | | |
| subjects affected / exposed | 3 / 3380 (0.09%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ankle fracture | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3380 (0.03%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 2 / 3380 (0.06%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 2 / 3380 (0.06%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radius fracture | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident | | | |
| subjects affected / exposed | 3 / 3380 (0.09%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Patella fracture | | | |
| subjects affected / exposed | 2 / 3380 (0.06%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3380 (0.00%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bite | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone fissure | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clavicle fracture | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis radiation | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaw fracture | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laceration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle rupture | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural complication | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pubis fracture | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin abrasion | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stab wound | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subarachnoid haematoma | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendon rupture | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (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 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tracheostomy malfunction | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fibula fracture | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| 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 | 12 / 3380 (0.36%) | 19 / 3377 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 12 | 1 / 19 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 4 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 11 / 3380 (0.33%) | 10 / 3377 (0.30%) | |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 4 / 3380 (0.12%) | 7 / 3377 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure | | | |
| subjects affected / exposed | 6 / 3380 (0.18%) | 5 / 3377 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Angina pectoris | | | |
| subjects affected / exposed | 4 / 3380 (0.12%) | 6 / 3377 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 4 / 3380 (0.12%) | 5 / 3377 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 3 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 3 / 3380 (0.09%) | 3 / 3377 (0.09%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 2 / 3380 (0.06%) | 4 / 3377 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute coronary syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 3380 (0.06%) | 3 / 3377 (0.09%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 3 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 3 / 3377 (0.09%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 3 / 3380 (0.09%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 2 / 3380 (0.06%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cor pulmonale | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 3380 (0.06%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive heart disease | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 2 / 3380 (0.06%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac asthma | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| 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 | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiovascular insufficiency | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cor pulmonale acute | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (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 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular hypertrophy | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Palpitations | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 8 / 3380 (0.24%) | 5 / 3377 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 4 / 3380 (0.12%) | 8 / 3377 (0.24%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 6 / 3380 (0.18%) | 5 / 3377 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 3 / 3377 (0.09%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral ischaemia | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3380 (0.03%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 3 / 3380 (0.09%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Partial seizures | | | |
| subjects affected / exposed | 2 / 3380 (0.06%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient global amnesia | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertebrobasilar insufficiency | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain stem haemorrhage | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain stem infarction | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular disorder | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular stenosis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dementia | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dementia Alzheimer's type | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial paralysis | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hemiparesis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrocephalus | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic cerebral infarction | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbosacral radiculopathy | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| 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 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertigo CNS origin | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vocal cord paralysis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vocal cord paresis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (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 | | | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polycythaemia | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo positional | | | |
| subjects affected / exposed | 3 / 3380 (0.09%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deafness neurosensory | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertigo | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vestibular disorder | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 4 / 3380 (0.12%) | 4 / 3377 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angle closure glaucoma | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dacryostenosis acquired | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Macular fibrosis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polypoidal choroidal vasculopathy | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 2 / 3380 (0.06%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 3380 (0.06%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic gastritis | | | |
| subjects affected / exposed | 2 / 3380 (0.06%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine polyp | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal hernia | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Change of bowel habit | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulum intestinal haemorrhagic | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric disorder | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mechanical ileus | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal varices haemorrhage | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic cyst | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Umbilical hernia | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Umbilical hernia, obstructive | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (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 / 3380 (0.03%) | 0 / 3377 (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 acute | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 4 / 3377 (0.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 3 / 3380 (0.09%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bile duct stone | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3380 (0.00%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis chronic persistent | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic foot | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pemphigus | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psoriasis | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin exfoliation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (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 | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 3 / 3380 (0.09%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 2 / 3380 (0.06%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| End stage renal disease | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive nephropathy | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal injury | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureterolithiasis | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urethral polyp | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary bladder haemorrhage | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Endocrine disorders** | | | |
| Autoimmune thyroiditis | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperparathyroidism | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxic nodular goitre | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (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** | | | |

| | | | |
|---|---|---|---|
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fracture delayed union | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| 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 | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Periarthritis | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rheumatoid arthritis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spondylolisthesis | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Trigger finger | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 19 / 3380 (0.56%) | 18 / 3377 (0.53%) | |
| occurrences causally related to treatment / all | 0 / 21 | 0 / 18 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 6 / 3380 (0.18%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 3380 (0.06%) | 5 / 3377 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |

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|---|---|---|---|
| subjects affected / exposed | 4 / 3380 (0.12%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 3 / 3377 (0.09%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Diabetic foot infection | | | |
| subjects affected / exposed | 3 / 3380 (0.09%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 2 / 3380 (0.06%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia klebsiella | | | |
| subjects affected / exposed | 2 / 3380 (0.06%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis infective | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dengue fever | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3380 (0.00%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gangrene | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Necrotising fasciitis | | | |
| subjects affected / exposed | 2 / 3380 (0.06%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia pseudomonal | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal bacteraemia | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Acinetobacter infection | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial infection | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial sepsis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cellulitis staphylococcal | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalitis viral | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epididymitis | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fungal skin infection | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gallbladder empyema | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Helicobacter gastritis | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hordeolum | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection parasitic | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral discitis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver abscess | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mastoiditis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis bacterial | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasal vestibulitis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Parasitic gastroenteritis | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Parotid abscess | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia staphylococcal | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis chronic | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue infection | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Splenic abscess | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tracheobronchitis | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tuberculosis | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (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 bacterial | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 2 / 3380 (0.06%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 3380 (0.06%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 2 / 3377 (0.06%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 2 / 3380 (0.06%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic ketoacidosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3380 (0.00%) | 1 / 3377 (0.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fluid overload | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemic hyperosmolar nonketotic syndrome | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 3380 (0.03%) | 0 / 3377 (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** | aQIV | Non-influenza Comparator Vaccine | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 227 / 3380 (6.72%) | 218 / 3377 (6.46%) | |
| General disorders and administration site conditions | | | |
| Pain | | | |
| subjects affected / exposed[1] | 106 / 253 (41.90%) | 77 / 193 (39.90%) | |
| occurrences (all) | 106 | 77 | |
| Erythema | | | |
| subjects affected / exposed[2] | 69 / 218 (31.65%) | 69 / 223 (30.94%) | |
| occurrences (all) | 69 | 69 | |
| Fatigue | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed[3] | 67 / 183 (36.61%) | 56 / 154 (36.36%) | |
| occurrences (all) | 67 | 56 | |
| Headache | | | |
| subjects affected / exposed[4] | 70 / 161 (43.48%) | 53 / 150 (35.33%) | |
| occurrences (all) | 70 | 53 | |
| Induration | | | |
| subjects affected / exposed[5] | 65 / 201 (32.34%) | 51 / 193 (26.42%) | |
| occurrences (all) | 65 | 51 | |
| Arthralgia | | | |
| subjects affected / exposed[6] | 47 / 138 (34.06%) | 42 / 129 (32.56%) | |
| occurrences (all) | 47 | 42 | |
| Myalgia | | | |
| subjects affected / exposed[7] | 49 / 134 (36.57%) | 39 / 109 (35.78%) | |
| occurrences (all) | 49 | 39 | |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Adverse events meeting reporting criteria were evaluated for a restricted per protocol subset of total subjects (solicited safety set).

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Adverse events meeting reporting criteria were evaluated for a restricted per protocol subset of total subjects (solicited safety set).

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Adverse events meeting reporting criteria were evaluated for a restricted per protocol subset of total subjects (solicited safety set).

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Adverse events meeting reporting criteria were evaluated for a restricted per protocol subset of total subjects (solicited safety set).

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Adverse events meeting reporting criteria were evaluated for a restricted per protocol subset of total subjects (solicited safety set).

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Adverse events meeting reporting criteria were evaluated for a restricted per protocol subset of total subjects (solicited safety set).

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Adverse events meeting reporting criteria were evaluated for a restricted per protocol subset of total subjects (solicited safety set).

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 19 June 2015 | Typographical corrections were made to remove inconsistencies across the document and the reference list was updated. |
| 16 December 2015 | The goal of this amendment was to simplify the protocol and to make it more focused on clinical benefit and the post-licensure commitments for Seqirus' adjuvanted TIV, FLUAD™, indicate sponsorship change, indicate reduction of burden to subjects and sites, and correction and clarification of protocol. |
| 29 March 2016 | The amendment included changes in blood sampling procedure and text updates. |
| 06 February 2017 | The amendment included addition of exploratory objectives, changes to analysis of age-related cohorts and to specified statistical analyses, and text corrections. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported