



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
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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
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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
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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
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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 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 Units: years			
arithmetic mean	71.9	71.8	-
standard deviation	± 5.53	± 5.36	
Gender categorical Units: Subjects			
Female	2105	2089	4194
Male	1289	1307	2596
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	615	607	1222
Not Hispanic or Latino	2773	2779	5552
Unknown or Not Reported	6	10	16
Race/Ethnicity 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 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			
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). 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). 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]
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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]
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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
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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]
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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
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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]
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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
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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
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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
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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
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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
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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
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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 $>37.2^{\circ}\text{C}/99^{\circ}\text{F}$, chills, tiredness, headache, or myalgia). Two additional definitions of ILI were used: modified CDC ILI definition defined as presence of fever (temperature $>37.2^{\circ}\text{C}$) with cough or sore throat and the WHO ILI definition consisting of fever (temperature $\geq 38.0^{\circ}\text{C}$) with cough. The WHO ILI definition was used in a post-hoc analysis. The FAS Efficacy was used for analysis.

End point type	Secondary
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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
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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
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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
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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
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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
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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
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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
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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 $>37.2^{\circ}\text{C}/99^{\circ}\text{F}$, chills, tiredness, headache, or myalgia). Two additional definitions of ILI were used: modified CDC ILI definition defined as presence of fever (temperature $>37.2^{\circ}\text{C}$) with cough or sore throat and the WHO ILI definition consisting of fever (temperature $\geq 38.0^{\circ}\text{C}$) 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
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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
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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
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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]
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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
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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

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]
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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
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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 $\geq 1:40$

End point title	Immunogenicity Endpoint: Percentages of Subjects With an HI Titer $\geq 1:40$ ^[7]
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End point description:

The percentage of subjects vaccinated with aQIV with a HI antibody titers $\geq 1:40$ 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 $\geq 1:40$ 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
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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]
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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 $\geq 1:40$ 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 $\geq 1:10$) 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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	aQIV
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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
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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			

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			

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			

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			

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			

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			

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			

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			

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			

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			

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			

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			

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			

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			

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			

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			

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			

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			

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			

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			

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