



Clinical trial results: Immunogenicity and Lot-to-Lot Consistency Study of a Quadrivalent Influenza Vaccine in Adult and Elderly Subjects

Summary

EudraCT number	2014-000785-21
Trial protocol	DE BE
Global end of trial date	23 October 2015

Results information

Result version number	v1 (current)
This version publication date	27 March 2016
First version publication date	27 March 2016

Trial information

Trial identification

Sponsor protocol code	GQM11
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1143-8801

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur SA
Sponsor organisation address	2, avenue Pont Pasteur, Lyon Cedex 07, France, F-69367
Public contact	Director, Clinical Development , Sanofi Pasteur SA, 33 4 37 37 5850, stephanie.pepin@sanofipasteur.com
Scientific contact	Director, Clinical Development , Sanofi Pasteur SA, 33 4 37 37 5850, stephanie.pepin@sanofipasteur.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	20 January 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Immunogenicity: Lot Consistency
To demonstrate equivalence of immune response induced by the 3 different industrial lots of Quadrivalent Influenza Vaccine (QIV) for each strain
- Immunogenicity: Non-inferiority
To demonstrate the non-inferiority of immune response induced by QIV compared with Trivalent Influenza Vaccine (TIV) for each strain

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were randomized and vaccinated in the study. Vaccinations were performed by qualified and trained study personnel. Subjects with allergy to any of the vaccine components were not vaccinated. After vaccination, subjects were also kept under clinical observation for 30 minutes to ensure their safety. Appropriate medical equipment was also available on site in case of any immediate allergic reactions.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	17 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 607
Country: Number of subjects enrolled	Belgium: 466
Country: Number of subjects enrolled	Germany: 587
Country: Number of subjects enrolled	France: 559
Worldwide total number of subjects	2219
EEA total number of subjects	2219

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)	1373
From 65 to 84 years	829
85 years and over	17

Subject disposition

Recruitment

Recruitment details:

The study subjects were enrolled from 17 September 2014 to 21 October 2014 at 3 clinic centers in Belgium, 3 in France, 4 in Germany, and 5 in Poland.

Pre-assignment

Screening details:

A total of 2225 subjects who met all of the inclusion and none of the exclusion criteria were randomized; however, 3 subjects were not injected and 3 subjects had no post-vaccination blood sample resulting in a total of 2219 patients.

Period 1

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

Blinding implementation details:

This was a double-blind study for subjects in the quadrivalent and trivalent influenza vaccine (TIV; Victoria) groups. The Investigator, the study staff, and the subject were blinded to study treatment. The study was a single-blind study up to Day 21 for all subjects included in the TIV (Yamagata) group. Immunogenicity was assessed in a blinded manner for all subjects. In the event of an emergency (i.e., serious adverse event), the code could be broken according to the code-breaking procedures.

Arms

Are arms mutually exclusive?	Yes
Arm title	QIV S4456

Arm description:

Subjects received a single dose of quadrivalent influenza vaccine (QIV) Lot 1 S4456.

Arm type	Experimental
Investigational medicinal product name	QIV (split-virion, inactivated)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular in the deltoid muscle or deep subcutaneous, 1 injection on Day 0.

Arm title	QIV S4457
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Arm description:

Subjects received a single dose of quadrivalent influenza vaccine (QIV) Lot 2 S4457.

Arm type	Experimental
Investigational medicinal product name	QIV (split-virion, inactivated)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular in the deltoid muscle or deep subcutaneous, 1 injection on Day 0.

Arm title	QIV S4458
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Arm description:

Subjects received a single dose of quadrivalent influenza vaccine (QIV) Lot 3 S4458.

Arm type	Experimental
Investigational medicinal product name	QIV (split-virion, inactivated)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular in the deltoid muscle or deep subcutaneous, 1 injection on Day 0.

Arm title	TIV1
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Arm description:

Subjects received a single dose of trivalent influenza vaccine (TIV) 1 from the Victoria lineage.

Arm type	Active comparator
Investigational medicinal product name	TIV1 (split-virion, inactivated) Victoria lineage
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular in the deltoid muscle or deep subcutaneous, 1 injection on Day 0.

Arm title	TIV2
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Arm description:

Subjects received a single dose of trivalent influenza vaccine (TIV) 2 from the Yamagata lineage.

Arm type	Active comparator
Investigational medicinal product name	TIV2 (split-virion, inactivated) Yamagata lineage
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular in the deltoid muscle or deep subcutaneous, 1 injection on Day 0.

Number of subjects in period 1	QIV S4456	QIV S4457	QIV S4458
Started	553	555	558
Completed	552	555	555
Not completed	1	0	3
Consent withdrawn by subject	-	-	2
Lost to follow-up	1	-	-
Protocol deviation	-	-	1

Number of subjects in period 1	TIV1	TIV2
Started	278	275
Completed	278	274
Not completed	0	1
Consent withdrawn by subject	-	-
Lost to follow-up	-	-

Protocol deviation	-	1
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Baseline characteristics

Reporting groups

Reporting group title	QIV S4456
Reporting group description:	
Subjects received a single dose of quadrivalent influenza vaccine (QIV) Lot 1 S4456.	
Reporting group title	QIV S4457
Reporting group description:	
Subjects received a single dose of quadrivalent influenza vaccine (QIV) Lot 2 S4457.	
Reporting group title	QIV S4458
Reporting group description:	
Subjects received a single dose of quadrivalent influenza vaccine (QIV) Lot 3 S4458.	
Reporting group title	TIV1
Reporting group description:	
Subjects received a single dose of trivalent influenza vaccine (TIV) 1 from the Victoria lineage.	
Reporting group title	TIV2
Reporting group description:	
Subjects received a single dose of trivalent influenza vaccine (TIV) 2 from the Yamagata lineage.	

Reporting group values	QIV S4456	QIV S4457	QIV S4458
Number of subjects	553	555	558
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)	344	330	350
From 65-84 years	204	221	204
85 years and over	5	4	4
Age continuous			
Units: years			
arithmetic mean	54.5	54.8	54.5
standard deviation	± 18.1	± 18.2	± 18.1
Gender categorical			
Units: Subjects			
Female	309	304	282
Male	244	251	276
History of influenza vaccination 2013/2014			
Number of subjects with a history of influenza vaccination by year			
Units: Subjects			
Influenza vaccination 2013/2014; Yes	187	196	195
Influenza vaccination 2013/2014; No	366	355	362

Influenza vaccination 2013/2014; Unknown	0	4	1
History of influenza vaccination 2012/2013 Units: Subjects			
Influenza vaccination 2012/2013; Yes	177	199	199
Influenza vaccination 2012/2013; No	373	355	356
Influenza vaccination 2012/2013; Unknown	3	1	3
History of influenza vaccination 2011/2012 Units: Subjects			
Influenza vaccination 2011/2012; Yes	179	209	197
Influenza vaccination 2011/2012; No	369	344	356
Influenza vaccination 2011/2012; Unknown	5	2	5

Reporting group values	TIV1	TIV2	Total
Number of subjects	278	275	2219
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)	176	172	1372
From 65-84 years	101	100	830
85 years and over	1	3	17
Age continuous Units: years			
arithmetic mean	55.6	53.7	-
standard deviation	± 16.9	± 18.6	
Gender categorical Units: Subjects			
Female	152	151	1198
Male	126	124	1021
History of influenza vaccination 2013/2014			
Number of subjects with a history of influenza vaccination by year			
Units: Subjects			
Influenza vaccination 2013/2014; Yes	102	89	769
Influenza vaccination 2013/2014; No	175	186	1444
Influenza vaccination 2013/2014; Unknown	1	0	6
History of influenza vaccination 2012/2013 Units: Subjects			

Influenza vaccination 2012/2013; Yes	105	97	777
Influenza vaccination 2012/2013; No	173	176	1433
Influenza vaccination 2012/2013; Unknown	0	2	9
History of influenza vaccination 2011/2012 Units: Subjects			
Influenza vaccination 2011/2012; Yes	104	94	783
Influenza vaccination 2011/2012; No	170	179	1418
Influenza vaccination 2011/2012; Unknown	4	2	18

Subject analysis sets

Subject analysis set title	Pooled QIV
Subject analysis set type	Full analysis
Subject analysis set description: Subjects received a single dose of either quadrivalent influenza vaccine (QIV) Lot 1 S4456, Lot 2 S4457, or Lot 3 S4458.	
Subject analysis set title	Pooled TIV
Subject analysis set type	Full analysis
Subject analysis set description: Subjects received a single dose of either trivalent influenza vaccine (TIV) 1 from the Victoria lineage or TIV 2 from the Yamagata lineage.	

Reporting group values	Pooled QIV	Pooled TIV	
Number of subjects	1666	553	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	1024	348	
From 65-84 years	629	201	
85 years and over	13	4	
Age continuous Units: years			
arithmetic mean	54.6	54.7	
standard deviation	± 18.1	± 17.8	
Gender categorical Units: Subjects			
Female	895	303	
Male	771	250	
History of influenza vaccination 2013/2014			
Number of subjects with a history of influenza vaccination by year			

Units: Subjects			
Influenza vaccination 2013/2014; Yes	578	191	
Influenza vaccination 2013/2014; No	1083	361	
Influenza vaccination 2013/2014; Unknown	5	1	
History of influenza vaccination 2012/2013			
Units: Subjects			
Influenza vaccination 2012/2013; Yes	575	202	
Influenza vaccination 2012/2013; No	1084	349	
Influenza vaccination 2012/2013; Unknown	7	2	
History of influenza vaccination 2011/2012			
Units: Subjects			
Influenza vaccination 2011/2012; Yes	585	198	
Influenza vaccination 2011/2012; No	1069	349	
Influenza vaccination 2011/2012; Unknown	12	6	

End points

End points reporting groups

Reporting group title	QIV S4456
Reporting group description: Subjects received a single dose of quadrivalent influenza vaccine (QIV) Lot 1 S4456.	
Reporting group title	QIV S4457
Reporting group description: Subjects received a single dose of quadrivalent influenza vaccine (QIV) Lot 2 S4457.	
Reporting group title	QIV S4458
Reporting group description: Subjects received a single dose of quadrivalent influenza vaccine (QIV) Lot 3 S4458.	
Reporting group title	TIV1
Reporting group description: Subjects received a single dose of trivalent influenza vaccine (TIV) 1 from the Victoria lineage.	
Reporting group title	TIV2
Reporting group description: Subjects received a single dose of trivalent influenza vaccine (TIV) 2 from the Yamagata lineage.	
Subject analysis set title	Pooled QIV
Subject analysis set type	Full analysis
Subject analysis set description: Subjects received a single dose of either quadrivalent influenza vaccine (QIV) Lot 1 S4456, Lot 2 S4457, or Lot 3 S4458.	
Subject analysis set title	Pooled TIV
Subject analysis set type	Full analysis
Subject analysis set description: Subjects received a single dose of either trivalent influenza vaccine (TIV) 1 from the Victoria lineage or TIV 2 from the Yamagata lineage.	

Primary: Geometric Mean Titers (GMTs) of Influenza Antibodies After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route in All Subjects

End point title	Geometric Mean Titers (GMTs) of Influenza Antibodies After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route in All Subjects
End point description: Anti-hemagglutinin antibody titers were measured for each strain with the seroneutralization method.	
End point type	Primary
End point timeframe: Day 21 post-vaccination	

End point values	Pooled QIV	Pooled TIV		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	830	278		
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
A/California/07/2009 (H1N1); 18 to 60 years	612 (567 to 661)	685 (587 to 800)		

A/California/07/2009 (H1N1); >60 years	219 (198 to 241)	268 (228 to 314)		
A/Texas/50/2012 (H3N2); 18 to 60 years	501 (461 to 544)	629 (543 to 728)		
A/Texas/50/2012 (H3N2); >60 years	359 (329 to 391)	410 (352 to 476)		
B/Brisbane/60/2008 (B Victoria); 18 to 60 years	708 (660 to 760)	735 (615 to 879)		
B/Brisbane/60/2008 (B Victoria); >60 years	287 (265 to 312)	301 (244 to 372)		
B/Massachusetts/02/2012 (B Yamagata); 18 to 60 yrs	1713 (1604 to 1829)	1735 (1490 to 2019)		
B/Massachusetts/02/2012 (B Yamagata); >60 yrs	656 (612 to 703)	697 (593 to 820)		

Statistical analyses

Statistical analysis title	Non-inferiority (A/H1N1; GMT Ratio; Overall)
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Statistical analysis description:

Ratio of GMTs were assessed in the H1N1 strain between the pooled QIV and TIV groups to determine non-inferiority.

Comparison groups	Pooled QIV v Pooled TIV
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
Parameter estimate	Ratio of GMTs
Point estimate	0.855
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.757
upper limit	0.968

Notes:

[1] - Non-inferiority was confirmed if the lower limit of the overall age-stratified two-sided 95% confidence interval of the ratio of geometric mean titers (GMTs) between groups (QIV/TIV) is >1/1.5 for each strain.

Statistical analysis title	Non-inferiority (A/H3N2; GMT Ratio; Overall)
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Statistical analysis description:

Ratio of GMTs were assessed in the H3N2 strain between the pooled QIV and TIV groups to determine non-inferiority.

Comparison groups	Pooled QIV v Pooled TIV
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
Parameter estimate	Ratio of GMTs
Point estimate	0.835
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.741
upper limit	0.941

Notes:

[2] - Non-inferiority was confirmed if the lower limit of the overall age-stratified two-sided 95% confidence interval of the ratio of geometric mean titers (GMTs) between groups (QIV/TIV) is $>1/1.5$ for each strain.

Statistical analysis title	Non-inferiority (B/Brisbane; GMT Ratio; Overall)
Statistical analysis description:	
Ratio of GMTs were assessed in the H1N1 strain between the pooled QIV and TIV groups to determine non-inferiority.	
Comparison groups	Pooled QIV v Pooled TIV
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
Parameter estimate	Ratio of GMTs
Point estimate	0.959
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.831
upper limit	1.11

Notes:

[3] - Non-inferiority was confirmed if the lower limit of the overall age-stratified two-sided 95% confidence interval of the ratio of geometric mean titers (GMTs) between groups (QIV/TIV) is $>1/1.5$ for each strain.

Statistical analysis title	Non-inferiority (B/Massachusetts; GMTR; Overall)
Statistical analysis description:	
Ratio of GMTs were assessed in the H3N2 strain between the pooled QIV and TIV groups to determine non-inferiority.	
Comparison groups	Pooled QIV v Pooled TIV
Number of subjects included in analysis	1108
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[4]
Parameter estimate	Ratio of GMTs
Point estimate	0.964
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.09

Notes:

[4] - Non-inferiority was confirmed if the lower limit of the overall age-stratified two-sided 95% confidence interval of the ratio of geometric mean titers (GMTs) between groups (QIV/TIV) is $>1/1.5$ for each strain.

Primary: Geometric Mean Titers (GMTs) of Influenza Antibodies Before and After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 18 to 60 years

End point title	Geometric Mean Titers (GMTs) of Influenza Antibodies Before and After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 18 to 60 years ^[5]
End point description:	
Anti-hemagglutinin antibody titers were measured for each strain with the seroneutralization method.	
End point type	Primary

End point timeframe:

Day 0 (pre-vaccination) and Day 21 post-vaccination

Notes:

[5] - 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: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	QIV S4456	QIV S4457	QIV S4458	TIV1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	277	276	280	140
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
A/H1N1; Day 0	59.7 (49.2 to 72.5)	63.5 (52.3 to 77.1)	63.6 (52.1 to 77.7)	57.4 (43.7 to 75.4)
A/H1N1; Day 21	603 (525 to 694)	649 (567 to 743)	575 (507 to 653)	737 (586 to 926)
A/H3N2; Day 0	47.5 (39 to 57.9)	47.7 (38.9 to 58.6)	50.5 (41.6 to 61.2)	39.6 (30.3 to 51.8)
A/H3N2; Day 21	526 (454 to 609)	487 (422 to 562)	484 (421 to 556)	583 (468 to 725)
B/Brisbane; Day 0	62.3 (52.3 to 74.2)	61.8 (51.4 to 74.3)	59.8 (50.4 to 71)	64.5 (50.1 to 83)
B/Brisbane; Day 21	711 (631 to 801)	723 (640 to 818)	692 (612 to 783)	735 (615 to 879)
B/Massachusetts; Day 0	213 (178 to 255)	249 (206 to 300)	240 (202 to 283)	214 (166 to 276)
B/Massachusetts; Day 21	1739 (1556 to 1944)	1736 (1550 to 1945)	1670 (1489 to 1874)	689 (556 to 854)

End point values	TIV2			
Subject group type	Reporting group			
Number of subjects analysed	138			
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
A/H1N1; Day 0	77.6 (58.9 to 102)			
A/H1N1; Day 21	637 (515 to 787)			
A/H3N2; Day 0	44.9 (34.1 to 59.1)			
A/H3N2; Day 21	680 (558 to 829)			
B/Brisbane; Day 0	67.1 (52.5 to 85.8)			
B/Brisbane; Day 21	204 (170 to 243)			
B/Massachusetts; Day 0	285 (222 to 365)			
B/Massachusetts; Day 21	1735 (1490 to 2019)			

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Titers (GMTs) of influenza Antibodies Before and After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 60 years and older

End point title	Geometric Mean Titers (GMTs) of influenza Antibodies Before and After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 60 years and older ^[6]
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End point description:

Anti-hemagglutinin antibody titers were measured for each strain with the seroneutralization method.

End point type	Primary
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End point timeframe:

Day 0 (pre-vaccination) and Day 21 post-vaccination

Notes:

[6] - 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: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	QIV S4456	QIV S4457	QIV S4458	TIV1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	276	277	279	138
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
A/H1N1; Day 0	42 (35.2 to 50)	48 (39.9 to 57.9)	43.3 (36 to 51.9)	53.5 (40.7 to 70.5)
A/H1N1; Day 21	222 (186 to 264)	216 (184 to 254)	219 (185 to 259)	328 (265 to 406)
A/H3N2; Day 0	59.3 (48.6 to 72.4)	70.3 (58 to 85.1)	63.2 (52.1 to 76.6)	79.8 (58.4 to 109)
A/H3N2; Day 21	362 (312 to 420)	395 (341 to 456)	324 (278 to 376)	492 (395 to 612)
B/Brisbane; Day 0	52.9 (44.3 to 63.1)	70.2 (58.5 to 84.4)	64.9 (54.8 to 76.9)	65.4 (51.1 to 83.7)
B/Brisbane; Day 21	272 (236 to 314)	314 (273 to 360)	277 (240 to 319)	301 (244 to 372)
B/Massachusetts; Day 0	140 (117 to 166)	156 (134 to 182)	186 (158 to 218)	172 (138 to 214)
B/Massachusetts; Day 21	595 (527 to 672)	661 (588 to 744)	712 (632 to 803)	351 (294 to 420)

End point values	TIV2			
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Subject group type	Reporting group			
Number of subjects analysed	137			
Units: Titers (1/dil)				
geometric mean (confidence interval 95%)				
A/H1N1; Day 0	36.7 (28.3 to 47.6)			
A/H1N1; Day 21	218 (171 to 277)			
A/H3N2; Day 0	62.6 (48.3 to 81.3)			
A/H3N2; Day 21	340 (276 to 419)			
B/Brisbane; Day 0	60.9 (47.9 to 77.4)			
B/Brisbane; Day 21	121 (101 to 147)			
B/Massachusetts; Day 0	170 (132 to 217)			
B/Massachusetts; Day 21	697 (593 to 820)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Aged 18 to 60 years With Seroprotection Against Influenza Antigens Before and After Vaccination Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Subjects Aged 18 to 60 years With Seroprotection Against Influenza Antigens Before and After Vaccination Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route ^[7]
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End point description:

Anti-hemagglutinin antibody titers were measured for each strain with the seroneutralization method. Seroprotection was defined as antibody titers ≥ 40 (1/dil).

End point type	Primary
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End point timeframe:

Day 0 (pre-vaccination) and Day 21 post-vaccination

Notes:

[7] - 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: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	QIV S4456	QIV S4457	QIV S4458	TIV1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	277	276	280	140
Units: Percentage of subjects				
number (not applicable)				
A/H1N1; Day 0	63.5	64.9	65.4	65.7
A/H1N1; Day 21	97.8	97.8	98.9	97.1
A/H3N2; Day 0	57.4	55.6	62.5	56.4

A/H3N2; Day 21	98.6	98.2	97.1	97.9
B/Brisbane; Day 0	62.5	61.5	61.8	67.9
B/Brisbane; Day 21	100	99.3	100	100
B/Massachusetts; Day 0	86.6	86.5	90.7	87.1
B/Massachusetts; Day 21	100	100	100	99.3

End point values	TIV2			
Subject group type	Reporting group			
Number of subjects analysed	138			
Units: Percentage of subjects				
number (not applicable)				
A/H1N1; Day 0	71			
A/H1N1; Day 21	97.1			
A/H3N2; Day 0	55.1			
A/H3N2; Day 21	99.3			
B/Brisbane; Day 0	65.2			
B/Brisbane; Day 21	97.8			
B/Massachusetts; Day 0	90.6			
B/Massachusetts; Day 21	100			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Aged 60 Years and Older With Seroprotection Against Influenza Antigens Before and After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Subjects Aged 60 Years and Older With Seroprotection Against Influenza Antigens Before and After Vaccination with a Quadrivalent Influenza Vaccine Administered via the Intramuscular Route ^[8]
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End point description:

Anti-hemagglutinin antibody titers were measured for each strain with the seroneutralization method. Seroprotection was defined as antibody titers ≥ 40 (1/dil).

End point type	Primary
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End point timeframe:

Day 0 (pre-vaccination) and Day 21 post-vaccination

Notes:

[8] - 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: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	QIV S4456	QIV S4457	QIV S4458	TIV1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	276	277	279	138
Units: Percentage of subjects				
number (not applicable)				
A/H1N1; Day 0	57.6	58.1	57.3	64.5
A/H1N1; Day 21	89.1	91.7	91	97.8
A/H3N2; Day 0	64.5	67	65.9	65.9
A/H3N2; Day 21	96	97.8	94.6	98.6
B/Brisbane; Day 0	59.8	69	69.1	70.3
B/Brisbane; Day 21	96.4	97.1	96	95.7
B/Massachusetts; Day 0	81.9	88	88.9	85.5
B/Massachusetts; Day 21	100	100	100	98.6

End point values	TIV2			
Subject group type	Reporting group			
Number of subjects analysed	137			
Units: Percentage of subjects				
number (not applicable)				
A/H1N1; Day 0	54			
A/H1N1; Day 21	91.2			
A/H3N2; Day 0	69.9			
A/H3N2; Day 21	97.1			
B/Brisbane; Day 0	66.4			
B/Brisbane; Day 21	85.4			
B/Massachusetts; Day 0	86.9			
B/Massachusetts; Day 21	100			

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Titer Ratios (GMTRs) of influenza Antibodies After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 18 to 60 years

End point title	Geometric Mean Titer Ratios (GMTRs) of influenza Antibodies After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 18 to 60 years ^[9]
End point description:	Anti-hemagglutinin antibody titers were measured for each strain with the seroneutralization method.
End point type	Primary
End point timeframe:	Day 21 post-vaccination/Day 0 (pre-vaccination)

Notes:

[9] - 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: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	QIV S4456	QIV S4457	QIV S4458	TIV1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	277	276	280	140
Units: Titer ratios (1/dil)				
geometric mean (confidence interval 95%)				
A/H1N1	10.1 (8.28 to 12.3)	10.2 (8.32 to 12.6)	9.04 (7.37 to 11.1)	12.8 (9.36 to 17.6)
A/H3N2	11.1 (9.07 to 13.5)	10.2 (8.32 to 12.5)	9.58 (7.87 to 11.7)	14.7 (10.9 to 19.8)
B/Brisbane	11.4 (9.44 to 13.8)	11.7 (9.66 to 14.2)	11.6 (9.59 to 14)	11.4 (8.66 to 15)
B/Massachusetts	8.17 (6.87 to 9.72)	6.97 (5.84 to 8.33)	6.97 (5.91 to 8.23)	3.22 (2.67 to 3.9)

End point values	TIV2			
Subject group type	Reporting group			
Number of subjects analysed	138			
Units: Titer ratios (1/dil)				
geometric mean (confidence interval 95%)				
A/H1N1	8.2 (6.27 to 10.7)			
A/H3N2	15.1 (11.2 to 20.4)			
B/Brisbane	3.03 (2.49 to 3.7)			
B/Massachusetts	6.08 (4.79 to 7.72)			

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Titer Ratios (GMTRs) of influenza Antibodies After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 60 years and older

End point title	Geometric Mean Titer Ratios (GMTRs) of influenza Antibodies After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 60 years and older ^[10]
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End point description:

Anti-hemagglutinin antibody titers were measured for each strain with the seroneutralization method.

End point type	Primary
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End point timeframe:

Day 21 post-vaccination/Day 0 (pre-vaccination)

Notes:

[10] - 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: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	QIV S4456	QIV S4457	QIV S4458	TIV1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	276	277	279	138
Units: Titer ratios (1/dil)				
geometric mean (confidence interval 95%)				
A/H1N1	5.29 (4.4 to 6.35)	4.5 (3.81 to 5.33)	5.06 (4.21 to 6.08)	6.13 (4.51 to 8.33)
A/H3N2	6.1 (5.01 to 7.43)	5.61 (4.67 to 6.75)	5.12 (4.24 to 6.18)	6.16 (4.53 to 8.39)
B/Brisbane	5.15 (4.33 to 6.13)	4.47 (3.77 to 5.3)	4.26 (3.61 to 5.03)	4.6 (3.5 to 6.05)
B/Massachusetts	4.26 (3.57 to 5.1)	4.24 (3.62 to 4.97)	3.83 (3.26 to 4.52)	2.04 (1.71 to 2.43)

End point values	TIV2			
Subject group type	Reporting group			
Number of subjects analysed	137			
Units: Titer ratios (1/dil)				
geometric mean (confidence interval 95%)				
A/H1N1	5.94 (4.56 to 7.72)			
A/H3N2	5.43 (4.22 to 6.99)			
B/Brisbane	1.99 (1.7 to 2.34)			
B/Massachusetts	4.11 (3.19 to 5.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Aged 18 to 60 Years Achieving Seroconversion or Significant increase Against Influenza Antigens after Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Subjects Aged 18 to 60 Years Achieving Seroconversion or Significant increase Against Influenza Antigens after Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route ^[11]
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End point description:

Anti-hemagglutinin antibody titers were measured for each strain with the seroneutralization method. Seroconversion was defined as the proportion of subjects with a pre-vaccination titer < 10 (1/dil) to a post-vaccination titer ≥ 40 (1/dil). Significant increase was defined as proportion of subjects with a pre-vaccination titer ≥ 10 (1/dil) and ≥ 4-fold increase of the titer.

End point type	Primary
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End point timeframe:

Day 21 post-vaccination/Day 0 (pre-vaccination)

Notes:

[11] - 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: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	QIV S4456	QIV S4457	QIV S4458	TIV1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	277	276	280	140
Units: Percentage of subjects				
number (not applicable)				
A/H1N1	65	65.6	61.8	63.6
A/H3N2	70.8	66.5	61.4	72.9
B/Brisbane	71.5	70.5	70.7	70
B/Massachusetts	67.1	61.1	62.9	42.1

End point values	TIV2			
Subject group type	Reporting group			
Number of subjects analysed	138			
Units: Percentage of subjects				
number (not applicable)				
A/H1N1	66.7			
A/H3N2	73.9			
B/Brisbane	38.4			
B/Massachusetts	60.9			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Aged 60 Years or Older Achieving Seroconversion or Significant increase Against Influenza Antigens after Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Given via the Intramuscular Route

End point title	Percentage of Subjects Aged 60 Years or Older Achieving Seroconversion or Significant increase Against Influenza Antigens after Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Given via the Intramuscular Route ^[12]
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End point description:

Anti-hemagglutinin antibody titers were measured for each strain with the seroneutralization method. Seroconversion was defined as the proportion of subjects with a pre-vaccination titer < 10 (1/dil) to a

post-vaccination titer ≥ 40 (1/dil). Significant increase was defined as proportion of subjects with a pre-vaccination titer ≥ 10 (1/dil) and ≥ 4 -fold increase of the titer.

End point type	Primary
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End point timeframe:

Day 21 post-vaccination/Day 0 (pre-vaccination)

Notes:

[12] - 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: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	QIV S4456	QIV S4457	QIV S4458	TIV1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	276	277	279	138
Units: Percentage of subjects				
number (not applicable)				
A/H1N1	49.3	43	44.4	48.6
A/H3N2	47.1	50.7	44.8	47.1
B/Brisbane	45.7	46.6	43.5	43.5
B/Massachusetts	42.8	45.3	40.1	28.3

End point values	TIV2			
Subject group type	Reporting group			
Number of subjects analysed	137			
Units: Percentage of subjects				
number (not applicable)				
A/H1N1	51.8			
A/H3N2	50			
B/Brisbane	21.2			
B/Massachusetts	38.7			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Aged 18 to 60 years Reporting Solicited Injection-site or Systemic Reaction After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Subjects Aged 18 to 60 years Reporting Solicited Injection-site or Systemic Reaction After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route ^[13]
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End point description:

Solicited injection site reactions: Pain, Erythema, Swelling, Induration, and Ecchymosis. Solicited systemic reactions: Fever, Headache, Malaise, Myalgia, and Shivering.

Grade 3 Solicited injection site reactions: Pain, Significant; prevents daily activity; Erythema, Swelling, Induration, and Ecchymosis > 100 mm. Grade 3 Solicited systemic reactions: Fever, $\geq 39.0^{\circ}\text{C}$; Headache, Malaise, Myalgia, and Shivering, Significant; prevents daily activity.

End point type	Primary
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End point timeframe:

Day 0 up to Day 7 post-vaccination

Notes:

[13] - 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: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	QIV S4456	QIV S4457	QIV S4458	TIV1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	277	276	280	140
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	53.1	57.2	53.9	48.6
Grade 3 Injection site Pain	0	0.7	0.4	0
Injection site Erythema	9	6.9	11.8	5
Grade 3 Injection site Erythema	0	0	0	0
Injection site Swelling	5.1	6.5	7.1	2.9
Grade 3 Injection site Swelling	0	0	0	0
Injection site Induration	4.3	6.9	8.2	4.3
Grade 3 Injection site Induration	0	0	0	0
Injection site Ecchymosis	0.7	0.7	0.7	0.7
Grade 3 Injection site Ecchymosis	0	0	0	0
Fever	0	0.7	1.4	0
Grade 3 Fever	0	0	0	0
Headache	26.4	27.2	26.4	23.6
Grade 3 Headache	0.7	3.3	1.1	0.7
Malaise	21.7	16.3	17.5	20.7
Grade 3 Malaise	1.1	2.5	0.7	0.7
Myalgia	24.5	25.7	28.6	17.9
Grade 3 Myalgia	0.4	0.4	0.7	1.4
Shivering	8.3	8.3	6.1	7.1
Grade 3 Shivering	0.7	0.4	0.7	0

End point values	TIV2			
Subject group type	Reporting group			
Number of subjects analysed	138			
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	61.6			
Grade 3 Injection site Pain	0.7			
Injection site Erythema	6.5			
Grade 3 Injection site Erythema	0.7			
Injection site Swelling	4.3			
Grade 3 Injection site Swelling	0			
Injection site Induration	6.5			
Grade 3 Injection site Induration	0			
Injection site Ecchymosis	0.7			
Grade 3 Injection site Ecchymosis	0			

Fever	0.7			
Grade 3 Fever	0			
Headache	30.4			
Grade 3 Headache	1.4			
Malaise	22.5			
Grade 3 Malaise	0.7			
Myalgia	23.9			
Grade 3 Myalgia	0			
Shivering	5.1			
Grade 3 Shivering	0			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Aged 60 years and older Reporting Solicited Injection-site or Systemic Reaction After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Subjects Aged 60 years and older Reporting Solicited Injection-site or Systemic Reaction After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route ^[14]
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End point description:

Solicited injection site reactions: Pain, Erythema, Swelling, Induration, and Ecchymosis. Solicited systemic reactions: Fever, Headache, Malaise, Myalgia, and Shivering.

Grade 3 Solicited injection site reactions: Pain, Significant; prevents daily activity; Erythema, Swelling, Induration, and Ecchymosis > 100 mm. Grade 3 Solicited systemic reactions: Fever, $\geq 39.0^{\circ}\text{C}$; Headache, Malaise, Myalgia, and Shivering, Significant; prevents daily activity.

End point type	Primary
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End point timeframe:

Day 0 up to Day 7 post-vaccination

Notes:

[14] - 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: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	QIV S4456	QIV S4457	QIV S4458	TIV1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	276	278	279	139
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	20.3	25.3	23.3	25.2
Grade 3 Injection site Pain	0	0.4	0	0
Injection site Erythema	8	9.4	5.4	7.9
Grade 3 Injection site Erythema	0	0	0	0.7
Injection site Swelling	3.3	4.3	2.2	2.9
Grade 3 Injection site Swelling	0	0	0	0
Injection site Induration	2.5	2.9	2.5	2.9
Grade 3 Injection site Induration	0	0	0	0

Injection site Ecchymosis	1.1	0.4	0	0
Grade 3 Injection site Ecchymosis	0	0	0	0
Fever	1.8	0.7	0.7	0
Grade 3 Fever	0.4	0.4	0	0
Headache	17	12.2	16.5	12.2
Grade 3 Headache	0.7	0.4	0.4	0
Malaise	12.7	9.4	9.3	10.1
Grade 3 Malaise	0	1.1	0.7	0
Myalgia	12	12.6	14	10.1
Grade 3 Myalgia	0	0.7	1.1	0
Shivering	3.3	4.3	5.7	3.6
Grade 3 Shivering	0.4	0	0.7	0.7

End point values	TIV2			
Subject group type	Reporting group			
Number of subjects analysed	137			
Units: Percentage of subjects				
number (not applicable)				
Injection site Pain	14.6			
Grade 3 Injection site Pain	0			
Injection site Erythema	5.8			
Grade 3 Injection site Erythema	0.7			
Injection site Swelling	3.6			
Grade 3 Injection site Swelling	0			
Injection site Induration	3.6			
Grade 3 Injection site Induration	0			
Injection site Ecchymosis	0.7			
Grade 3 Injection site Ecchymosis	0			
Fever	0.7			
Grade 3 Fever	0			
Headache	11.7			
Grade 3 Headache	0.7			
Malaise	12.4			
Grade 3 Malaise	1.5			
Myalgia	13.1			
Grade 3 Myalgia	0			
Shivering	4.4			
Grade 3 Shivering	0			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Aged 18 to 60 Years Reporting Solicited Reactions Listed in the EMA Note for Guidance within 3 Days After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Given via the Intramuscular Route

End point title	Percentage of Subjects Aged 18 to 60 Years Reporting Solicited Reactions Listed in the EMA Note for Guidance within 3 Days After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Given via the Intramuscular Route ^[15]
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End point description:

Reactions listed in the European Medicines Agency (EMA) Note for Guidance: Injection site induration ≥ 5 cm for at least 4 consecutive days; Injection site ecchymosis (injection site bruising); Pyrexia (recorded temperature > 38.0°C) for at least 1 day; Malaise; Shivering (Rigors).

End point type	Primary
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End point timeframe:

Day 0 up to Day 3 post-vaccination

Notes:

[15] - 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: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	QIV S4456	QIV S4457	QIV S4458	TIV1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	277	276	280	140
Units: Percentage of subjects				
number (not applicable)				
Reaction listed in the EMA recommendations	22.7	19.9	18.2	20
Injection site Induration ≥ 5 cm for 4 days	0	0	0	0
Injection site Ecchymosis	2.2	2.2	3.2	2.1
Pyrexia (> 38.0°C) for at least 1 day	0	0.4	1.1	0
Malaise	18.8	14.5	13.9	17.1
Shivering (Rigors)	7.2	7.2	5.7	6.4

End point values	TIV2			
Subject group type	Reporting group			
Number of subjects analysed	138			
Units: Percentage of subjects				
number (not applicable)				
Reaction listed in the EMA recommendations	19.6			
Injection site Induration ≥ 5 cm for 4 days	0			
Injection site Ecchymosis	2.9			
Pyrexia (> 38.0°C) for at least 1 day	0			
Malaise	15.2			
Shivering (Rigors)	3.6			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Aged 60 years and older Reporting Solicited Reactions Listed in the EMA Note for Guidance within 3 Days of Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Given via the Intramuscular Route

End point title	Percentage of Subjects Aged 60 years and older Reporting Solicited Reactions Listed in the EMA Note for Guidance within 3 Days of Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Given via the Intramuscular Route ^[16]
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End point description:

Reactions listed in the European Medicines Agency (EMA) Note for Guidance: Injection site induration \geq 5 cm for at least 4 consecutive days; Injection site ecchymosis (injection site bruising); Pyrexia (recorded temperature $> 38.0^{\circ}\text{C}$) for at least 1 day; Malaise; Shivering (Rigors).

End point type	Primary
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End point timeframe:

Day 0 up to Day 3 post-vaccination

Notes:

[16] - 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: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

End point values	QIV S4456	QIV S4457	QIV S4458	TIV1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	276	278	279	139
Units: Percentage of subjects				
number (not applicable)				
Reaction listed in the EMA recommendations	13	10.4	11.5	7.9
Injection site Induration \geq 5 cm for 4 days	0	0	0.4	0
Injection site Ecchymosis	2.5	4	1.1	1.4
Pyrexia ($> 38.0^{\circ}\text{C}$) for at least 1 day	0.7	0.7	0.4	0
Malaise	10.5	6.8	7.5	7.2
Shivering (Rigors)	2.5	4	4.7	2.2

End point values	TIV2			
Subject group type	Reporting group			
Number of subjects analysed	137			
Units: Percentage of subjects				
number (not applicable)				
Reaction listed in the EMA recommendations	11.7			
Injection site Induration \geq 5 cm for 4 days	0			
Injection site Ecchymosis	2.9			
Pyrexia ($> 38.0^{\circ}\text{C}$) for at least 1 day	0			
Malaise	8.8			
Shivering (Rigors)	2.2			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects Aged 18 to 60 years With Seroprotection Against Influenza Antigens Before and After Vaccination Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Subjects Aged 18 to 60 years With Seroprotection Against Influenza Antigens Before and After Vaccination Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route
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End point description:

Anti-hemagglutinin antibody titers were measured for each strain with the seroneutralization method. Seroprotection was defined as antibody titers ≥ 40 (1/dil).

End point type	Other pre-specified
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End point timeframe:

Day 0 (pre-vaccination) and Day 21 post-vaccination

End point values	Pooled QIV	Pooled TIV		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	833	278		
Units: Percentage				
number (not applicable)				
A/H1N1; Day 0	64.6	68.3		
A/H1N1; Day 21	98.2	97.1		
A/H3N2; Day 0	58.5	55.8		
A/H3N2; Day 21	98	98.6		
B/Brisbane; Day 0	61.9	67.9		
B/Brisbane; Day 21	99.8	100		
B/Massachusetts; Day 0	88	90.6		
B/Massachusetts; Day 21	100	100		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects Aged 60 years and Older With Seroprotection Against Influenza Antigens Before and After Vaccination Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Subjects Aged 60 years and Older With Seroprotection Against Influenza Antigens Before and After Vaccination Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route
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End point description:

Anti-hemagglutinin antibody titers were measured for each strain with the seroneutralization method. Seroprotection was defined as antibody titers ≥ 40 (1/dil).

End point type	Other pre-specified
End point timeframe:	
Day 0 (pre-vaccination) and Day 21 post-vaccination	

End point values	Pooled QIV	Pooled TIV		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	832	275		
Units: Percentage				
number (not applicable)				
A/H1N1; Day 0	57.7	59.3		
A/H1N1; Day 21	90.6	94.5		
A/H3N2; Day 0	65.8	67.9		
A/H3N2; Day 21	96.1	97.8		
B/Brisbane; Day 0	65.9	70.3		
B/Brisbane; Day 21	96.5	95.7		
B/Massachusetts; Day 0	86.3	86.9		
B/Massachusetts; Day 21	100	100		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Geometric Mean Titers of influenza Antibodies Before and After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 18 to 60 years.

End point title	Geometric Mean Titers of influenza Antibodies Before and After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 18 to 60 years.
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End point description:

Anti-hemagglutinin antibody titers were measured for each strain with the seroneutralization method

End point type	Other pre-specified
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End point timeframe:

Day 0 (pre-vaccination); Day 21; Day 180 and Day 365 post-vaccination

End point values	Pooled QIV	Pooled TIV		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	145	70		
Units: Geometric Mean Titers				
geometric mean (confidence interval 95%)				
A/H1N1; Day 0	68.7 (52.2 to 90.5)	65.2 (45.9 to 92.6)		
A/H1N1; Day 21	658 (565 to 767)	681 (501 to 925)		

A/H1N1; Day 180	290 (244 to 345)	253 (189 to 339)		
A/H1N1; Day 365	250 (208 to 301)	207 (151 to 285)		
A/H3N2; Day 0	47.8 (36.8 to 62.1)	42 (29.5 to 59.7)		
A/H3N2; Day 21	470 (386 to 571)	703 (517 to 955)		
A/H3N2; Day 180	225 (185 to 274)	275 (206 to 366)		
A/H3N2; Day 365	184 (150 to 226)	202 (149 to 273)		
B/Brisbane; Day 0	58.7 (45.3 to 76.1)	57.2 (33.2 to 98.6)		
B/Brisbane; Day 21	675 (575 to 793)	718 (462 to 1118)		
B/Brisbane; Day 180	285 (235 to 346)	271 (179 to 409)		
B/Brisbane; Day 365	248 (199 to 309)	217 (142 to 332)		
B/Massachusetts; Day 0	197 (153 to 254)	256 (175 to 374)		
B/Massachusetts; Day 21	1731 (1492 to 2009)	1759 (1341 to 2307)		
B/Massachusetts; Day 180	830 (684 to 1007)	873 (637 to 1197)		
B/Massachusetts; Day 365	685 (558 to 840)	764 (551 to 1059)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Geometric Mean Titers of influenza Antibodies Before and After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 60 years and older.

End point title	Geometric Mean Titers of influenza Antibodies Before and After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 60 years and older.
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End point description:

Anti-hemagglutinin antibody titers were measured for each strain with the seroneutralization method

End point type	Other pre-specified
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End point timeframe:

Day 0 (pre-vaccination); Day 21; Day 180 and Day 365 post-vaccination.

End point values	Pooled QIV	Pooled TIV		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	145	70		
Units: Geometric Mean Titers				
geometric mean (confidence interval 95%)				
A/H1N1; Day 0	42.7 (33.4 to 54.4)	45.5 (30.7 to 67.4)		
A/H1N1; Day 21	204 (162 to 257)	240 (176 to 327)		
A/H1N1; Day 180	87.3 (68.8 to 111)	120 (86.4 to 167)		
A/H1N1; Day 365	77.4 (60.8 to 98.7)	107 (75.5 to 153)		
A/H3N2; Day 0	63.9 (48 to 85)	79.6 (52.8 to 120)		
A/H3N2; Day 21	392 (317 to 484)	404 (293 to 557)		
A/H3N2; Day 180	180 (144 to 225)	221 (155 to 314)		
A/H3N2; Day 365	144 (113 to 182)	144 (101 to 205)		
B/Brisbane; Day 0	64.5 (50.5 to 82.5)	55.7 (33.5 to 92.7)		
B/Brisbane; Day 21	281 (233 to 340)	282 (161 to 493)		
B/Brisbane; Day 180	132 (108 to 161)	147 (85.2 to 253)		
B/Brisbane; Day 365	118 (93.9 to 147)	117 (73 to 188)		
B/Massachusetts; Day 0	169 (135 to 212)	182 (117 to 284)		
B/Massachusetts; Day 21	667 (563 to 789)	645 (497 to 836)		
B/Massachusetts; Day 180	340 (284 to 407)	334 (247 to 451)		
B/Massachusetts; Day 365	324 (272 to 387)	340 (249 to 463)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Geometric Mean Titer Ratios of influenza Antibodies After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 18 to 60 years

End point title	Geometric Mean Titer Ratios of influenza Antibodies After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 18 to 60 years
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End point description:

Anti-hemagglutinin antibody titers were measured for each strain with the seroneutralization method.

End point type	Other pre-specified
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End point timeframe:

Day 0 (pre-vaccination); Day 21; Day 180 and Day 365 post-vaccination

End point values	Pooled QIV	Pooled TIV		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	148	78		
Units: Geometric Mean Titer Ratios				
geometric mean (confidence interval 95%)				
A/H1N1; Day 21/Day 0	9.58 (7.21 to 12.7)	10.4 (7.25 to 15)		
A/H1N1; Day 180/Day 21	0.441 (0.388 to 0.5)	0.373 (0.324 to 0.43)		
A/H1N1; Day 365/Day 21	0.361 (0.31 to 0.421)	0.324 (0.275 to 0.382)		
A/H3N2; Day 21/Day 0	9.83 (7.62 to 12.7)	16.7 (11.4 to 24.6)		
A/H3N2; Day 180/Day 21	0.479 (0.414 to 0.555)	0.377 (0.303 to 0.468)		
A/H3N2; Day 365/Day 21	0.382 (0.328 to 0.446)	0.277 (0.218 to 0.353)		
B/Brisbane; Day 21/Day 0	11.5 (8.88 to 14.9)	12.6 (6.81 to 23.1)		
B/Brisbane; Day 180/Day 21	0.422 (0.38 to 0.47)	0.366 (0.28 to 0.48)		
B/Brisbane; Day 365/Day 21	0.352 (0.308 to 0.402)	0.275 (0.201 to 0.377)		
B/Massachusetts; Day 21/Day 0	8.79 (7.01 to 11)	6.87 (4.85 to 9.74)		
Massachusetts; Day 180/Day 21	0.479 (0.432 to 0.532)	0.496 (0.415 to 0.594)		
Massachusetts; Day 365/Day 21	0.407 (0.361 to 0.459)	0.454 (0.362 to 0.569)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Geometric Mean Titer Ratios of influenza Antibodies After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 60 years and older

End point title	Geometric Mean Titer Ratios of influenza Antibodies After Vaccination with Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route in Subjects Aged 60 years and older
End point description:	Anti-hemagglutinin antibody titers were measured for each strain with the seroneutralization method.
End point type	Other pre-specified
End point timeframe:	Day 0 (pre-vaccination); Day 21; Day 180 and Day 365 post-vaccination.

End point values	Pooled QIV	Pooled TIV		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	145	70		
Units: Geometric Mean Titer Ratios				
geometric mean (confidence interval 95%)				
A/H1N1; Day 21/Day 0	4.77 (3.84 to 5.94)	5.28 (3.57 to 7.8)		
A/H1N1; Day 180/Day 21	0.431 (0.376 to 0.494)	0.508 (0.403 to 0.64)		
A/H1N1; Day 365/Day 21	0.358 (0.313 to 0.411)	0.422 (0.317 to 0.56)		
A/H3N2; Day 21/Day 0	6.14 (4.64 to 8.11)	5.07 (3.48 to 7.39)		
A/H3N2; Day 180/Day 21	0.46 (0.387 to 0.548)	0.554 (0.423 to 0.724)		
A/H3N2; Day 365/Day 21	0.359 (0.298 to 0.434)	0.376 (0.288 to 0.493)		
B/Brisbane; Day 21/Day 0	4.39 (3.55 to 5.44)	5.07 (2.37 to 10.8)		
B/Brisbane; Day 180/Day 21	0.465 (0.417 to 0.518)	0.555 (0.388 to 0.793)		
B/Brisbane; Day 365/Day 21	0.423 (0.373 to 0.481)	0.443 (0.303 to 0.648)		
B/Massachusetts; Day 21/Day 0	3.94 (3.15 to 4.94)	3.54 (2.27 to 5.52)		
B/Massachusetts; Day 180/Day 21	0.51 (0.454 to 0.573)	0.518 (0.424 to 0.634)		
B/Massachusetts; Day 365/Day 21	0.475 (0.416 to 0.542)	0.53 (0.42 to 0.671)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects Aged 18 to 60 years With Seroprotection Against Influenza Antigens Before and After Vaccination Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Subjects Aged 18 to 60 years With Seroprotection Against Influenza Antigens Before and After Vaccination Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route
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End point description:

Anti-hemagglutinin antibody titers were measured for each strain with the seroneutralization method. Seroprotection was defined as antibody titers ≥ 40 (1/dil).

End point type	Other pre-specified
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End point timeframe:

Day 0 (pre-vaccination); Day 21; Day 180 and Day 365 post-vaccination

End point values	Pooled QIV	Pooled TIV		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	148	78		
Units: Percentage				
number (not applicable)				
A/H1N1; Day 0	67.6	70.5		
A/H1N1; Day 21	98.6	97.4		
A/H1N1; Day 180	96.6	90.9		
A/H1N1; Day 365	94.5	89.7		
A/H3N2; Day 0	60.8	60.3		
A/H3N2; Day 21	97.3	98.7		
A/H3N2; Day 180	92.6	93.5		
A/H3N2; Day 365	91.4	92.5		
B/Brisbane; Day 0	58.1	73.3		
B/Brisbane; Day 21	100	100		
B/Brisbane; Day 180	97.3	100		
B/Brisbane; Day 365	95.3	100		
B/Massachusetts; Day 0	85.1	91.7		
B/Massachusetts; Day 21	100	100		
B/Massachusetts; Day 180	100	100		
B/Massachusetts; Day 365	99.2	100		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects Aged 60 years and Older With Seroprotection Against Influenza Antigens Before and After Vaccination Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route

End point title	Percentage of Subjects Aged 60 years and Older With Seroprotection Against Influenza Antigens Before and After Vaccination Either a Quadrivalent Influenza Vaccine or a Trivalent Influenza Vaccine Administered via the Intramuscular Route
End point description: Anti-hemagglutinin antibody titers were measured for each strain with the seroneutralization method. Seroprotection was defined as antibody titers ≥ 40 (1/dil).	
End point type	Other pre-specified
End point timeframe: Day 0 (pre-vaccination); Day 21; Day 180 and Day 365 post-vaccination	

End point values	Pooled QIV	Pooled TIV		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	145	70		
Units: Percentage				
number (not applicable)				
A/H1N1; Day 0	57.9	58.6		
A/H1N1; Day 21	89.7	94.3		
A/H1N1; Day 180	76.2	85.3		
A/H1N1; Day 365	75	80.3		
A/H3N2; Day 0	65.5	71.4		
A/H3N2; Day 21	94.5	97.1		
A/H3N2; Day 180	89.5	92.6		
A/H3N2; Day 365	85.9	83.6		
B/Brisbane; Day 0	66.9	72.7		
B/Brisbane; Day 21	97.2	100		
B/Brisbane; Day 180	89.5	95		
B/Brisbane; Day 365	83.6	95		
B/Massachusetts; Day 0	86.2	85.4		
B/Massachusetts; Day 21	100	100		
B/Massachusetts; Day 180	100	100		
B/Massachusetts; Day 365	100	100		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected from Day 0 up to 12 months post-vaccination.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14
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Reporting groups

Reporting group title	QIV S4456
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Reporting group description:

Subjects received a single dose of quadrivalent influenza vaccine (QIV) Lot 1 S4456.

Reporting group title	QIV S4457
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Reporting group description:

Subjects received a single dose of quadrivalent influenza vaccine (QIV) Lot 2 S4457.

Reporting group title	QIV S4458
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Reporting group description:

Subjects received a single dose of quadrivalent influenza vaccine (QIV) Lot 3 S4458.

Reporting group title	TIV1
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Reporting group description:

Subjects received a single dose of trivalent influenza vaccine (TIV) 1 from the Victoria lineage.

Reporting group title	TIV2
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Reporting group description:

Subjects received a single dose of trivalent influenza vaccine (TIV) 2 from the Yamagata lineage.

Serious adverse events	QIV S4456	QIV S4457	QIV S4458
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 554 (3.43%)	12 / 554 (2.17%)	14 / 560 (2.50%)
number of deaths (all causes)	1	1	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anaplastic astrocytoma			
subjects affected / exposed	0 / 554 (0.00%)	1 / 554 (0.18%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic lymphocytic leukaemia			

subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial cancer			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal carcinoma			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metastatic neoplasm			
subjects affected / exposed	0 / 554 (0.00%)	1 / 554 (0.18%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid neoplasm			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	1 / 560 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aneurysm			
subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			

subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicose vein			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	1 / 560 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Rotator cuff repair			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Hyperemesis gravidarum			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 554 (0.00%)	1 / 554 (0.18%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	1 / 560 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Confusional state			
subjects affected / exposed	0 / 554 (0.00%)	1 / 554 (0.18%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	1 / 560 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus lesion			
subjects affected / exposed	0 / 554 (0.00%)	1 / 554 (0.18%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 554 (0.00%)	1 / 554 (0.18%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Tendon rupture			
subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 554 (0.00%)	1 / 554 (0.18%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	1 / 560 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	0 / 554 (0.00%)	1 / 554 (0.18%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	1 / 560 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sick sinus syndrome			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	1 / 560 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 554 (0.00%)	1 / 554 (0.18%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	0 / 554 (0.00%)	1 / 554 (0.18%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	1 / 560 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Cataract			
subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Maculopathy			
subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	1 / 560 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal polyp			
subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis chronic			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	1 / 560 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			

subjects affected / exposed	0 / 554 (0.00%)	1 / 554 (0.18%)	2 / 560 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	1 / 560 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	2 / 554 (0.36%)	0 / 554 (0.00%)	1 / 560 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scleroderma			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	1 / 560 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Erysipelas			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin abscess			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 554 (0.00%)	1 / 554 (0.18%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pilonidal cyst			
subjects affected / exposed	0 / 554 (0.00%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	1 / 560 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 554 (0.18%)	0 / 554 (0.00%)	0 / 560 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	TIV1	TIV2	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 279 (3.23%)	6 / 275 (2.18%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anaplastic astrocytoma			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	0 / 279 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal carcinoma			

subjects affected / exposed	1 / 279 (0.36%)	0 / 275 (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 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid neoplasm			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aneurysm			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			

Rotator cuff repair			
subjects affected / exposed	1 / 279 (0.36%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Hyperemesis gravidarum			
subjects affected / exposed	1 / 279 (0.36%)	0 / 275 (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			
Asthma			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			

subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	1 / 279 (0.36%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 279 (0.36%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	0 / 279 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus lesion			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina unstable			
subjects affected / exposed	1 / 279 (0.36%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			

subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 279 (0.36%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 279 (0.36%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Maculopathy			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal polyp			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 279 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			

subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scleroderma			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 279 (0.36%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	0 / 279 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	0 / 279 (0.00%)	1 / 275 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 279 (0.00%)	0 / 275 (0.00%)	
occurrences causally related to treatment / all	0 / 0	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	QIV S4456	QIV S4457	QIV S4458
Total subjects affected by non-serious adverse events			
subjects affected / exposed	147 / 554 (26.53%)	158 / 554 (28.52%)	151 / 560 (26.96%)
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed ^[1]	73 / 277 (26.35%)	75 / 276 (27.17%)	74 / 280 (26.43%)
occurrences (all)	73	75	74
General disorders and administration site conditions			
Injection site Pain			
alternative assessment type: Systematic			
subjects affected / exposed ^[2]	147 / 277 (53.07%)	158 / 276 (57.25%)	151 / 280 (53.93%)
occurrences (all)	147	158	151
Injection site Erythema			
alternative assessment type: Systematic			
subjects affected / exposed ^[3]	25 / 277 (9.03%)	26 / 278 (9.35%)	33 / 280 (11.79%)
occurrences (all)	25	26	33
Injection site Swelling			
alternative assessment type: Systematic			
subjects affected / exposed ^[4]	14 / 277 (5.05%)	18 / 276 (6.52%)	20 / 280 (7.14%)
occurrences (all)	14	18	20
Injection site Induration			
alternative assessment type: Systematic			
subjects affected / exposed ^[5]	12 / 277 (4.33%)	19 / 276 (6.88%)	23 / 280 (8.21%)
occurrences (all)	12	19	23
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed ^[6]	60 / 277 (21.66%)	45 / 276 (16.30%)	49 / 280 (17.50%)
occurrences (all)	60	45	49
Shivering			
alternative assessment type: Systematic			

subjects affected / exposed ^[7] occurrences (all)	23 / 277 (8.30%) 23	23 / 276 (8.33%) 23	17 / 280 (6.07%) 17
Musculoskeletal and connective tissue disorders Myalgia alternative assessment type: Systematic subjects affected / exposed ^[8] occurrences (all)	68 / 277 (24.55%) 68	71 / 276 (25.72%) 71	80 / 280 (28.57%) 80
Infections and infestations Nasopharyngitis subjects affected / exposed ^[9] occurrences (all)	19 / 552 (3.44%) 19	19 / 554 (3.43%) 20	16 / 560 (2.86%) 17

Non-serious adverse events	TIV1	TIV2	
Total subjects affected by non-serious adverse events subjects affected / exposed	68 / 279 (24.37%)	85 / 275 (30.91%)	
Nervous system disorders Headache alternative assessment type: Systematic subjects affected / exposed ^[1] occurrences (all)	33 / 140 (23.57%) 33	42 / 138 (30.43%) 42	
General disorders and administration site conditions Injection site Pain alternative assessment type: Systematic subjects affected / exposed ^[2] occurrences (all)	68 / 140 (48.57%) 68	85 / 138 (61.59%) 85	
Injection site Erythema alternative assessment type: Systematic subjects affected / exposed ^[3] occurrences (all)	11 / 139 (7.91%) 11	9 / 138 (6.52%) 9	
Injection site Swelling alternative assessment type: Systematic subjects affected / exposed ^[4] occurrences (all)	4 / 140 (2.86%) 4	6 / 138 (4.35%) 6	
Injection site Induration alternative assessment type: Systematic			

subjects affected / exposed ^[5] occurrences (all)	6 / 140 (4.29%) 6	9 / 138 (6.52%) 9	
Malaise alternative assessment type: Systematic subjects affected / exposed ^[6] occurrences (all)	29 / 140 (20.71%) 29	31 / 138 (22.46%) 31	
Shivering alternative assessment type: Systematic subjects affected / exposed ^[7] occurrences (all)	10 / 140 (7.14%) 10	7 / 138 (5.07%) 7	
Musculoskeletal and connective tissue disorders Myalgia alternative assessment type: Systematic subjects affected / exposed ^[8] occurrences (all)	25 / 140 (17.86%) 25	33 / 138 (23.91%) 33	
Infections and infestations Nasopharyngitis subjects affected / exposed ^[9] occurrences (all)	11 / 279 (3.94%) 11	9 / 275 (3.27%) 9	

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: This was a solicited adverse event recorded in a diary card within 7 days after vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[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: This was a solicited adverse event recorded in a diary card within 7 days after vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[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: This was a solicited adverse event recorded in a diary card within 7 days after vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[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: This was a solicited adverse event recorded in a diary card within 7 days after vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[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: This was a solicited adverse event recorded in a diary card within 7 days after vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[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: This was a solicited adverse event recorded in a diary card within 7 days after vaccination;

the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[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: This was a solicited adverse event recorded in a diary card within 7 days after vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[8] - 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: This was a solicited adverse event recorded in a diary card within 7 days after vaccination; the total number (N) reflects those subjects for which the diary cards were returned and for which data were available for the event during the period.

[9] - 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: This was an unsolicited adverse event recorded in a diary card within 21 days after vaccination; the total number (N) reflects those subjects for which data were available for the event during the period.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 November 2014	Included an additional blood sample collection to be used to test the persistence of the immune response and the informed consent form was updated to inform the subjects of the observational subset, addition of a 4th visit, and to obtain their consent to continue in the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported