Clinical trial results:
Immunogenicity and Safety of a High-Dose Quadrivalent Influenza Vaccine Administered by the Intramuscular Route in Subjects 60 Years of Age and Older

Summary

EudraCT number	2019-000655-14
Trial protocol	FR BE DE NL IT
Global end of trial date	05 June 2020

Results information

Result version number	v1 (current)
This version publication date	17 March 2021
First version publication date	17 March 2021

Trial information

Trial identification

Sponsor protocol code	QHD00011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04024228
WHO universal trial number (UTN)	U1111-1225-0952

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur
Sponsor organisation address	14, Espace Henry Vallée, Lyon, France, 69007
Public contact	Trial Transparency Team, Sanofi Pasteur, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi Pasteur, Contact-US@sanofi.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	14 May 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that High-Dose Quadrivalent Influenza Vaccine (QIV-HD) induces an immune response that is superior to the responses induced by Standard-Dose Quadrivalent Influenza Vaccine (QIV-SD) for all 4 virus strains 28 days post-vaccination in subjects 60 to 64 years of age and in subjects 65 years of age and older.

Protection of trial subjects:

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: -

Evidence for comparator: -

Actual start date of recruitment	28 October 2019
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	Netherlands: 344
Country: Number of subjects enrolled	Poland: 300
Country: Number of subjects enrolled	Belgium: 212
Country: Number of subjects enrolled	France: 271
Country: Number of subjects enrolled	Germany: 327
Country: Number of subjects enrolled	Italy: 85
Worldwide total number of subjects	1539
EEA total number of subjects	1539

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)	760
From 65 to 84 years	769
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 17 active centers in 6 countries. A total of 1539 subjects were enrolled and randomised between 28 October 2019 to 15 November 2019.

Pre-assignment

Screening details:

A total of 1533 subjects were vaccinated in the study.

Period 1

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

Blinding implementation details:

Modified double-blind: the subject and the investigators remained unaware of the treatment assignments throughout the study. An unblinded qualified trial staff member administered the appropriate vaccine but were not involved in the immunogenicity and safety evaluations.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1: QIV-HD

Arm description:

Subjects received a single injection of 0.7 millilitres (mL) QIV-HD, intramuscularly (IM) at Day 0.

Arm type	Experimental
Investigational medicinal product name	High-Dose Quadrivalent Influenza Vaccine (split virion, inactivated)
Investigational medicinal product code	QIV-HD
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.7 mL single injection at Day 0.

Arm title	Group 2: QIV-SD

Arm description:

Subjects received a single injection of 0.5 mL QIV-SD, IM at Day 0.

Arm type	Active comparator
Investigational medicinal product name	Standard-Dose Quadrivalent Influenza Vaccine (Inactivated)
Investigational medicinal product code	QIV-SD
Other name	Influvac™ Tetra
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL single injection at Day 0.

Number of subjects in period 1	Group 1: QIV-HD	Group 2: QIV-SD
Started	774	765
Vaccinated	772	761
Full Analysis Set (FAS)	769 [1]	758 [2]
Completed	770	759
Not completed	4	6
Adverse Event	1	-
Withdrawal by Subject	3	4
Protocol deviation	-	2

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: FAS included all randomised subjects who received the study vaccine and had a post-vaccination blood sample. 377 subjects (60-64 years) and 392 subjects (>=65 years).

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: FAS included all randomised subjects who received the study vaccine and had a post-vaccination blood sample. 377 subjects (60-64 years) and 381 subjects (>=65 years).

Baseline characteristics

Reporting groups	
Reporting group title	Group 1: QIV-HD
Reporting group description:	
Subjects received a single injection of 0.7 millilitres (mL) QIV-HD, intramuscularly (IM) at Day 0.	
Reporting group title	Group 2: QIV-SD
Reporting group description:	
Subjects received a single injection of 0.5 mL QIV-SD, IM at Day 0.	

Reporting group values	Group 1: QIV-HD	Group 2: QIV-SD	Total
Number of subjects	774	765	1539
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	66.6	66.6	
standard deviation	± 5.82	± 6.11	-
Gender categorical Units: Subjects			
Female	385	390	775
Male	389	375	764
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	4	3	7
Native Hawaiian or Other Pacific Islander	4	2	6
Black or African American	2	2	4
White	758	756	1514
More than one race	0	1	1
Unknown or Not Reported	6	1	7

End points

End points reporting groups

Reporting group title	Group 1: QIV-HD
Reporting group description:	
Subjects received a single injection of 0.7 millilitres (mL) QIV-HD, intramuscularly (IM) at Day 0.	
Reporting group title	Group 2: QIV-SD
Reporting group description:	
Subjects received a single injection of 0.5 mL QIV-SD, IM at Day 0.	

Primary: Geometric Mean Titers (GMTs) of Influenza Antibodies in Subjects Aged 60-64 Years and Greater Than or Equal to (>=) 65 Years

End point title	Geometric Mean Titers (GMTs) of Influenza Antibodies in Subjects Aged 60-64 Years and Greater Than or Equal to (>=) 65 Years
End point description:	
GMTs of anti-influenza antibodies were measured using hemagglutination inhibition (HAI) assay for 4 influenza virus strains: A/H1N1, A/H3N2, B1 (B Victoria lineage), and B2 (B Yamagata lineage). Titers were expressed in terms of 1/dilution. Analysis was performed on FAS population. Here, 'n' = subjects with available data for each specified category.	
End point type	Primary
End point timeframe:	
Day 28 post-vaccination	

End point values	Group 1: QIV-HD	Group 2: QIV-SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	769	758		
Units: titers				
geometric mean (confidence interval 95%)				
A/H1N1: Day 28: 60-64 years (n=377,377)	471 (416 to 533)	248 (217 to 283)		
A/H3N2: Day 28: 60-64 years (n=376,377)	303 (262 to 350)	178 (154 to 206)		
B1: Day 28: 60-64 years (n=377,377)	497 (450 to 548)	330 (297 to 367)		
B2: Day 28: 60-64 years (n=377,377)	766 (690 to 849)	433 (391 to 480)		
A/H1N1: Day 28: >= 65 years (n=392,381)	286 (250 to 326)	162 (139 to 190)		
A/H3N2: Day 28: >=65 years (n=392,381)	324 (281 to 374)	151 (129 to 176)		
B1: Day 28: >=65 years (n=392,381)	405 (366 to 447)	262 (236 to 291)		
B2: Day 28: >=65 years (n=392,381)	536 (485 to 592)	305 (274 to 340)		

Statistical analyses

Statistical analysis title	A/H1N1: 60-64 years
Comparison groups	Group 1: QIV-HD v Group 2: QIV-SD
Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	superiority[1]
Parameter estimate	GMT ratio
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.58
upper limit	2.28

Notes:

[1] - Superiority of GMTs was concluded if the lower limit of the 2-sided 95% Confidence Interval (CI) for the ratio of GMTs was above 1 between groups for each of the comparisons.

Statistical analysis title	A/H3N2: 60-64 years
Comparison groups	Group 1: QIV-HD v Group 2: QIV-SD
Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	superiority[2]
Parameter estimate	GMT ratio
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.38
upper limit	2.08

Notes:

[2] - Superiority of GMTs was concluded if the lower limit of the 2-sided 95% CI for the ratio of GMTs was above 1 between groups for each of the comparisons.

Statistical analysis title	B1: 60-64 years
Comparison groups	Group 1: QIV-HD v Group 2: QIV-SD
Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	superiority[3]
Parameter estimate	GMT ratio
Point estimate	1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	1.74

Notes:

[3] - Superiority of GMTs was concluded if the lower limit of the 2-sided 95% CI for the ratio of GMTs was above 1 between groups for each of the comparisons.

Statistical analysis title	B2: 60-64 years
Comparison groups	Group 1: QIV-HD v Group 2: QIV-SD

Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	superiority[4]
Parameter estimate	GMT ratio
Point estimate	1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.53
upper limit	2.04

Notes:

[4] - Superiority of GMTs was concluded if the lower limit of the 2-sided 95% CI for the ratio of GMTs was above 1 between groups for each of the comparisons.

Statistical analysis title	A/H1N1: >=65 years
Comparison groups	Group 1: QIV-HD v Group 2: QIV-SD
Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	superiority[5]
Parameter estimate	GMT ratio
Point estimate	1.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.44
upper limit	2.15

Notes:

[5] - Superiority of GMTs was concluded if the lower limit of the 2-sided 95% CI for the ratio of GMTs was above 1 between groups for each of the comparisons.

Statistical analysis title	A/H3N2: >=65 years
Comparison groups	Group 1: QIV-HD v Group 2: QIV-SD
Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	superiority[6]
Parameter estimate	GMT ratio
Point estimate	2.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.74
upper limit	2.65

Notes:

[6] - Superiority of GMTs was concluded if the lower limit of the 2-sided 95% CI for the ratio of GMTs was above 1 between groups for each of the comparisons.

Statistical analysis title	B1: >=65 years
Comparison groups	Group 1: QIV-HD v Group 2: QIV-SD

Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	superiority[7]
Parameter estimate	GMT ratio
Point estimate	1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.34
upper limit	1.79

Notes:

[7] - Superiority of GMTs was concluded if the lower limit of the 2-sided 95% CI for the ratio of GMTs was above 1 between groups for each of the comparisons.

Statistical analysis title	B1: >=65 years
Comparison groups	Group 1: QIV-HD v Group 2: QIV-SD
Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	superiority[8]
Parameter estimate	GMT ratio
Point estimate	1.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.52
upper limit	2.03

Notes:

[8] - Superiority of GMTs was concluded if the lower limit of the 2-sided 95% CI for the ratio of GMTs was above 1 between groups for each of the comparisons.

Secondary: Geometric Mean Titers of Influenza Antibodies Pre-and Post-Vaccination in All Age Group Subjects

End point title	Geometric Mean Titers of Influenza Antibodies Pre-and Post-Vaccination in All Age Group Subjects

End point description:

GMTs of anti-influenza antibodies were measured using HAI assay for 4 influenza virus strains: A/H1N1, A/H3N2, B1 (B Victoria lineage), and B2 (B Yamagata lineage). Titers were expressed in terms of 1/dilution. Analysis was performed on FAS population. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination), Day 28 (post-vaccination)

End point values	Group 1: QIV-HD	Group 2: QIV-SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	769	758		
Units: titers				
geometric mean (confidence interval 95%)				
A/H1N1: Day 0 (n=768,758)	48.6 (43.4 to 54.4)	46.2 (41.4 to 51.7)		

A/H1N1: Day 28 (n=769,758)	365 (333 to 400)	200 (181 to 222)		
A/H3N2: Day 0 (n=767,757)	13.3 (12.3 to 14.4)	13.0 (12.0 to 14.1)		
A/H3N2: Day 28 (n=768,758)	313 (283 to 347)	164 (148 to 182)		
B1: Day 0 (n=767,757)	63.9 (57.7 to 70.7)	74.5 (67.3 to 82.4)		
B1: Day 28 (n=769,758)	447 (417 to 480)	294 (272 to 316)		
B2: Day 0 (n=765,755)	89.7 (80.5 to 99.9)	96.6 (86.9 to 107)		
B2: Day 28 (n=769,758)	638 (594 to 686)	363 (337 to 392)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers of Influenza Antibodies Pre- and Post-Vaccination in Subjects Aged 60-64 Years and >=65 Years

End point title	Geometric Mean Titers of Influenza Antibodies Pre- and Post-Vaccination in Subjects Aged 60-64 Years and >=65 Years

End point description:

GMTs of anti-influenza antibodies were measured using HAI assay for 4 influenza virus strains: A/H1N1, A/H3N2, B1 (B Victoria lineage), and B2 (B Yamagata lineage). Titers were expressed in terms of 1/dilution. Analysis was performed on FAS population. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination), Day 28 (post-vaccination)

End point values	Group 1: QIV-HD	Group 2: QIV-SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	769	758		
Units: titers				
geometric mean (confidence interval 95%)				
A/H1N1: Day 0: 60-64 years (n=376,377)	50.2 (42.7 to 59.0)	50.0 (42.6 to 58.8)		
A/H1N1: Day 28: 60-64 years (n=377,377)	471 (416 to 533)	248 (217 to 283)		
A/H3N2: Day 0: 60-64 years (n=376,377)	11.5 (10.4 to 12.8)	12.5 (11.2 to 14.0)		
A/H3N2: Day 28: 60-64 years (n=376,377)	303 (262 to 350)	178 (154 to 206)		
B1: Day 0: 60-64 years (n=377,377)	54.7 (47.4 to 63.2)	68.7 (59.4 to 79.5)		
B1: Day 28: 60-64 years (n=377,377)	497 (450 to 548)	330 (297 to 367)		
B2: Day 0: 60-64 years (n=377,375)	80.4 (68.6 to 94.3)	93.2 (79.5 to 109)		

B2: Day 28: 60-64 years (n=377,377)	766 (690 to 849)	433 (391 to 480)		
A/H1N1: Day 0: >=65 years (n=392,381)	47.1 (40.1 to 55.2)	42.8 (36.6 to 50.0)		
A/H1N1: Day 28: >=65 years (n=392,381)	286 (250 to 326)	162 (139 to 190)		
A/H3N2: Day 0: >=65 years (n=391,380)	15.2 (13.5 to 17.1)	13.5 (12.1 to 15.0)		
A/H3N2: Day 0: >=65 years (n=392,381)	324 (281 to 374)	151 (129 to 176)		
B1: Day 0: >=65 years (n=390,380)	74.2 (64.3 to 85.6)	80.7 (70.1 to 92.9)		
B1: Day 28: >=65 years (n=392,381)	405 (366 to 447)	262 (236 to 291)		
B2: Day 0: >=65 years (n=388,380)	99.7 (86.1 to 115)	100 (86.8 to 115)		
B2: Day 28: >=65 years (n=392,381)	536 (485 to 592)	305 (274 to 340)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titer Ratios (GMTRs) of Influenza Antibodies in All Age Group Subjects

End point title	Geometric Mean Titer Ratios (GMTRs) of Influenza Antibodies in All Age Group Subjects

End point description:

GMTRs of anti-influenza antibodies were measured using HAI assay for 4 influenza virus strains: A/H1N1, A/H3N2, B1 (B Victoria lineage), and B2 (B Yamagata lineage). GMTRs were calculated as the ratio of GMTs post-vaccination (on Day 28) and pre-vaccination (on Day 0). Analysis was performed on FAS population. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination), Day 28 (post-vaccination)

End point values	Group 1: QIV-HD	Group 2: QIV-SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	769	758		
Units: ratio				
geometric mean (confidence interval 95%)				
A/H1N1: Day 28/Day 0 (n=768,758)	7.50 (6.68 to 8.42)	4.34 (3.88 to 4.84)		
A/H3N2: Day 28/Day 0 (n=767,757)	23.7 (21.4 to 26.1)	12.6 (11.3 to 14.0)		
B1: Day 28/Day 0 (n=767,757)	7.02 (6.34 to 7.77)	3.95 (3.56 to 4.38)		
B2: Day 28/Day 0 (n=765,755)	7.13 (6.44 to 7.90)	3.77 (3.42 to 4.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titer Ratios of Influenza Antibodies in Subjects Aged 60-64 Years and >=65 Years

End point title	Geometric Mean Titer Ratios of Influenza Antibodies in Subjects Aged 60-64 Years and >=65 Years

End point description:

GMTRs of anti-influenza antibodies were measured using HAI assay for 4 influenza virus strains: A/H1N1, A/H3N2, B1 (B Victoria lineage), and B2 (B Yamagata lineage). GMTRs were calculated as the ratio of GMTs post-vaccination (on Day 28) and pre-vaccination (on Day 0). Analysis was performed on FAS population. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination), Day 28 (post-vaccination)

End point values	Group 1: QIV-HD	Group 2: QIV-SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	769	758		
Units: ratio				
geometric mean (confidence interval 95%)				
A/H1N1: Day 28/Day 0: 60-64 years (n=376,377)	9.36 (7.86 to 11.1)	4.96 (4.20 to 5.85)		
A/H3N2: Day 28/Day 0: 60-64 years (n=376,377)	26.2 (22.8 to 30.2)	14.2 (12.2 to 16.6)		
B1: Day 28/Day 0: 60-64 years (n=377,377)	9.07 (7.84 to 10.5)	4.80 (4.11 to 5.60)		
B2: Day 28/Day 0: 60-64 years (n=377,375)	9.52 (8.19 to 11.1)	4.66 (4.03 to 5.39)		
A/H1N1: Day 28/Day 0: >=65 years (n=392,381)	6.07 (5.22 to 7.05)	3.80 (3.27 to 4.41)		
A/H3N2: Day 28/Day 0: >=65 years (n=391,380)	21.4 (18.6 to 24.7)	11.2 (9.66 to 13.0)		
B1: Day 28/Day 0: >=65 years (n=390,380)	5.48 (4.78 to 6.28)	3.25 (2.83 to 3.73)		
B2: Day 28/Day 0: >=65 years (n=388,380)	5.39 (4.72 to 6.15)	3.06 (2.70 to 3.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects (All Age Group Subjects) With Neutralising Antibody Titers >=40 (1/Dilution)

End point title	Percentage of Subjects (All Age Group Subjects) With Neutralising Antibody Titers >=40 (1/Dilution)

End point description:

Neutralising Antibody titer was measured using HAI assay method for 4 influenza virus strains: A/H1N1, A/H3N2, B1 (B Victoria lineage), and B2 (B Yamagata lineage). Percentage of subjects (all age group subjects) with neutralising antibody titers >=40 (1/dilution) is reported in the end-point. Analysis was performed on FAS population. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Day 28 post-vaccination

End point values	Group 1: QIV-HD	Group 2: QIV-SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	769	758		
Units: percentage of subjects				
number (confidence interval 95%)				
A/H1N1: Day 28 (n=769,758)	96.6 (95.1 to 97.8)	88.4 (85.9 to 90.6)		
A/H3N2: Day 28 (n=768,758)	93.8 (91.8 to 95.4)	86.4 (83.8 to 88.8)		
B1: Day 28 (n=769,758)	99.5 (98.7 to 99.9)	99.2 (98.3 to 99.7)		
B2: Day 28 (n=769,758)	99.5 (98.7 to 99.9)	98.3 (97.1 to 99.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects (Aged 60-64 Years and >=65 Years) With Neutralising Antibody Titers >=40 (1/Dilution)

End point title	Percentage of Subjects (Aged 60-64 Years and >=65 Years) With Neutralising Antibody Titers >=40 (1/Dilution)

End point description:

Neutralising Antibody titer was measured using HAI assay method for 4 influenza virus strains: A/H1N1, A/H3N2, B1 (B Victoria lineage), and B2 (B Yamagata lineage). Percentage of subjects (aged 60-64 Years and >=65 Years) with neutralising antibody titers >=40 (1/dilution) is reported in the endpoint. Analysis was performed on FAS population. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Day 28 post-vaccination

End point values	Group 1: QIV-HD	Group 2: QIV-SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	769	758		
Units: percentage of subjects				
number (confidence interval 95%)				
A/H1N1: Day 28: 60-64 years (n=377,377)	98.1 (96.2 to 99.3)	92.3 (89.1 to 94.8)		
A/H3N2: Day 28: 60-64 years (n=376,377)	94.9 (92.2 to 96.9)	89.1 (85.5 to 92.1)		
B1: Day 28: 60-64 years (n=377,377)	100 (99.0 to 100)	99.5 (98.1 to 99.9)		
B2: Day 28: 60-64 years (n=377,377)	99.7 (98.5 to 100)	99.5 (98.1 to 99.9)		
A/H1N1: Day 28: >=65 years (n=392,381)	95.2 (92.5 to 97.1)	84.5 (80.5 to 88.0)		
A/H3N2: Day 28: >=65 years (n=392,381)	92.6 (89.5 to 95.0)	83.7 (79.6 to 87.3)		
B1: Day 28: >=65 years (n=392,381)	99.0 (97.4 to 99.7)	99.0 (97.3 to 99.7)		
B2: Day 28: >=65 years (n=392,381)	99.2 (97.8 to 99.8)	97.1 (94.9 to 98.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects (All Age Group Subjects) Achieving Seroconversion Against Antigens

End point title	Percentage of Subjects (All Age Group Subjects) Achieving Seroconversion Against Antigens

End point description:

Anti-influenza antibodies were measured by HAI assay for 4 influenza virus strains: A/H1N1, A/H3N2, B1 (B Victoria lineage), and B2 (B Yamagata lineage). Seroconversion was defined as either a pre-vaccination HAI titer less than (<) 1:10 (1/dilution) and a post-vaccination titer >=1:40 (1/dilution) or a pre-vaccination titer >= 1:10 (1/dilution) and a >= four-fold increase in post-vaccination titer at Day 28. Percentage of subjects (all age group subjects) achieving seroconversion is reported in the endpoint. Analysis was performed on FAS population. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Day 28 post-vaccination

End point values	Group 1: QIV-HD	Group 2: QIV-SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	769	758		
Units: percentage of subjects				
number (confidence interval 95%)				
A/H1N1: Day 28 (n=768,758)	62.1 (58.6 to 65.6)	39.2 (35.7 to 42.8)		

A/H3N2: Day 28 (n=767,757)	88.1 (85.6 to 90.3)	74.2 (71.0 to 77.3)		
B1: Day 28 (n=767,757)	62.5 (58.9 to 65.9)	41.2 (37.7 to 44.8)		
B2: Day 28 (n=765,755)	62.7 (59.2 to 66.2)	41.6 (38.0 to 45.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects (Aged 60-64 Years and >=65 Years) Achieving Seroconversion Against Antigens

End point title	Percentage of Subjects (Aged 60-64 Years and >=65 Years) Achieving Seroconversion Against Antigens

End point description:

Anti-influenza antibodies were measured by HAI assay for 4 influenza virus strains: A/H1N1, A/H3N2, B1 (B Victoria lineage), and B2 (B Yamagata lineage). Seroconversion was defined as either a pre-vaccination HAI titer < 1:10 (1/dilution) and a post-vaccination titer >= 1:40 (1/dilution) or a pre-vaccination titer >= 1:10 (1/dilution) and a >= four-fold increase in post-vaccination titer at Day 28. Percentage of subjects (aged 60-64 Years and >=65 Years) achieving seroconversion is reported in the endpoint. Analysis was performed on FAS population. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Day 28 post-vaccination

End point values	Group 1: QIV-HD	Group 2: QIV-SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	769	758		
Units: percentage of subjects				
number (confidence interval 95%)				
A/H1N1: Day 28: 60-64 years (n=376,377)	66.5 (61.5 to 71.2)	41.4 (36.4 to 46.5)		
A/H3N2: Day 28: 60-64 years (n=376,377)	89.4 (85.8 to 92.3)	76.7 (72.1 to 80.8)		
B1: Day 28: 60-64 years (n=377,377)	68.2 (63.2 to 72.8)	47.7 (42.6 to 52.9)		
B2: Day 28: 60-64 years (n=377,375)	70.6 (65.7 to 75.1)	48.5 (43.4 to 53.7)		
A/H1N1: Day 28: >=65 years (n=392,381)	57.9 (52.8 to 62.8)	37.0 (32.1 to 42.1)		
A/H3N2: Day 28: >=65 years (n=391,380)	87.0 (83.2 to 90.1)	71.8 (67.0 to 76.3)		
B1: Day 28: >=65 years (n=390,380)	56.9 (51.8 to 61.9)	34.7 (30.0 to 39.8)		
B2: Day 28: >=65 years (n=388,380)	55.2 (50.1 to 60.2)	34.7 (30.0 to 39.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Immediate Unsolicited Adverse Events (AEs)

End point title	Number of Subjects Reporting Immediate Unsolicited Adverse Events (AEs)

End point description:

An AE was any untoward medical occurrence in a patient or in a clinical investigation subject administered a medicinal product and which did not had any casual relationship with the treatment. An unsolicited AE was an observed AE that did not fulfill the conditions prelisted in the case report book (CRB) in terms of diagnosis and/or onset window post-vaccination. All subjects were observed for 30 minutes after vaccination, and any unsolicited AEs occurred during that time were recorded as immediate unsolicited AEs in the CRB. Analysis was performed on safety analysis set (SafAS) which included subjects who had received the study vaccine and had any safety data available.

End point type	Secondary

End point timeframe:

Within 30 minutes post-vaccination

End point values	Group 1: QIV-HD	Group 2: QIV-SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	772	761		
Units: subjects				
number (not applicable)	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Solicited Injection Site Reactions

End point title	Number of Subjects Reporting Solicited Injection Site Reactions

End point description:

A solicited reaction (SR) was an expected adverse reaction (sign or symptom) observed and reported under the conditions (nature and onset) prelisted (i.e., solicited) in the CRB and considered as related to the product administered. Solicited injection site reactions included induration, bruising, pain, erythema, and swelling. Analysis was performed on the SafAS population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Within 7 days post-vaccination

End point values	Group 1: QIV-HD	Group 2: QIV-SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	770	759		
Units: subjects				
number (not applicable)				
Bruising	12	7		
Erythema	157	85		
Induration	132	64		
Pain	350	159		
Swelling	140	62		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Solicited Systemic Reactions

End point title	Number of Subjects Reporting Solicited Systemic Reactions

End point description:

A SR was an expected adverse reaction (sign or symptom) observed and reported under the conditions (nature and onset) prelisted (i.e., solicited) in the CRB and considered as related to the product administered. Solicited systemic reactions included fever, headache, malaise, myalgia and shivering. Analysis was performed on the SafAS population. Here, 'number of subjects analysed' = subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Within 7 days post-vaccination

End point values	Group 1: QIV-HD	Group 2: QIV-SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	770	759		
Units: subjects				
number (not applicable)				
Fever	18	4		
Headache	184	141		
Malaise	164	89		
Myalgia	202	93		
Shivering	128	54		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Unsolicited Adverse Events (AEs)

End point title	Number of Subjects Reporting Unsolicited Adverse Events (AEs)

End point description:

An AE was any untoward medical occurrence in a patient or in a clinical investigation subject administered a medicinal product and which did not had any casual relationship with the treatment. An unsolicited AE was an observed AE that did not fulfill the conditions prelisted in the case report book (CRB) in terms of diagnosis and/or onset window post-vaccination. Analysis was performed on SafAS population.

End point type	Secondary

End point timeframe:

Within 28 days post-vaccination

End point values	Group 1: QIV-HD	Group 2: QIV-SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	772	761		
Units: subjects				
number (not applicable)	190	172		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Serious Adverse Events (SAEs) Including Adverse Event of Special Interest (AESIs)

End point title	Number of Subjects Reporting Serious Adverse Events (SAEs) Including Adverse Event of Special Interest (AESIs)

End point description:

A SAE was any untoward medical occurrence that at any dose resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or was an important medical event. A SAE which caused death of the subject was considered as fatal SAE. Adverse events of special interest (AESIs) was defined as event for which ongoing monitoring and rapid communication by the investigator to the sponsor was done. Analysis was performed on the SafAS population.

End point type	Secondary

End point timeframe:

From Day 0 up to 6 months post-vaccination

End point values	Group 1: QIV-HD	Group 2: QIV-SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	772	761		
Units: subjects				
number (not applicable)				
SAE	17	21		
AESI	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Unsolicited AEs were collected from Day 0 (post-vaccination) up to 28 days post-vaccination. SR data were collected up to Day 7 post-vaccination. SAE data were collected throughout the study, i.e. up to 6 months post-vaccination.

Adverse event reporting additional description:

Safety analysis set. SR was an adverse reaction that was prelisted (i.e., solicited) in CRB and considered to be related to vaccination. Unsolicited AE was an observed AE that did not fulfill the conditions prelisted in CRB in terms of diagnosis and/or onset window post-vaccination. In AE section, SR shivering were reported as chills.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Group 1: QIV-HD

Reporting group description:

Subjects received a single injection of 0.7 mL QIV-HD, IM at Day 0.

Reporting group title	Group 2: QIV-SD

Reporting group description:

Subjects received a single injection of 0.5 mL QIV-SD, IM at Day 0.

Serious adverse events	Group 1: QIV-HD	Group 2: QIV-SD	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 772 (2.20%)	21 / 761 (2.76%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast Cancer			
subjects affected / exposed	1 / 772 (0.13%)	0 / 761 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial Carcinoma			
subjects affected / exposed	1 / 772 (0.13%)	0 / 761 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial Cancer			

subjects affected / exposed	1 / 772 (0.13%)	0 / 761 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polycythaemia Vera			
subjects affected / exposed	0 / 772 (0.00%)	1 / 761 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid Neoplasm			
subjects affected / exposed	0 / 772 (0.00%)	1 / 761 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Forearm Fracture			
subjects affected / exposed	1 / 772 (0.13%)	0 / 761 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus Fracture			
subjects affected / exposed	0 / 772 (0.00%)	1 / 761 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus Injury			
subjects affected / exposed	0 / 772 (0.00%)	1 / 761 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road Traffic Accident			
subjects affected / exposed	1 / 772 (0.13%)	0 / 761 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thermal Burn			
subjects affected / exposed	0 / 772 (0.00%)	1 / 761 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Intermittent Claudication			
subjects affected / exposed	1 / 772 (0.13%)	0 / 761 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	1 / 772 (0.13%)	0 / 761 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Stenosis			
subjects affected / exposed	0 / 772 (0.00%)	1 / 761 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	0 / 772 (0.00%)	2 / 761 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral Thrombosis			
subjects affected / exposed	1 / 772 (0.13%)	0 / 761 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			
subjects affected / exposed	0 / 772 (0.00%)	1 / 761 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss Of Consciousness			
subjects affected / exposed	0 / 772 (0.00%)	1 / 761 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	1 / 772 (0.13%)	1 / 761 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vith Nerve Paralysis			
subjects affected / exposed	0 / 772 (0.00%)	1 / 761 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric Perforation			
subjects affected / exposed	0 / 772 (0.00%)	1 / 761 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Haemorrhage			
subjects affected / exposed	1 / 772 (0.13%)	0 / 761 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Obstruction			
subjects affected / exposed	0 / 772 (0.00%)	1 / 761 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestinal Obstruction			
subjects affected / exposed	1 / 772 (0.13%)	0 / 761 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage			
subjects affected / exposed	0 / 772 (0.00%)	1 / 761 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Prolapse			
subjects affected / exposed	0 / 772 (0.00%)	1 / 761 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 772 (0.13%)	0 / 761 (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			
Pulmonary Embolism			
subjects affected / exposed	1 / 772 (0.13%)	0 / 761 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 772 (0.00%)	1 / 761 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Incontinence			
subjects affected / exposed	0 / 772 (0.00%)	1 / 761 (0.13%)	
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			
Rheumatoid Arthritis			
subjects affected / exposed	0 / 772 (0.00%)	1 / 761 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendonitis			
subjects affected / exposed	0 / 772 (0.00%)	1 / 761 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Corona Virus Infection			
subjects affected / exposed	2 / 772 (0.26%)	1 / 761 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal Cyst			
subjects affected / exposed	1 / 772 (0.13%)	0 / 761 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal Sepsis			

subjects affected / exposed	1 / 772 (0.13%)	0 / 761 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 772 (0.13%)	0 / 761 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 772 (0.13%)	0 / 761 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Group 1: QIV-HD	Group 2: QIV-SD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	507 / 772 (65.67%)	354 / 761 (46.52%)	
Nervous system disorders			
Headache	Additional description: Headache events that occurred after 7 days post-vaccination were considered as unsolicited AE.		
subjects affected / exposed	190 / 772 (24.61%)	149 / 761 (19.58%)	
occurrences (all)	196	156	
General disorders and administration site conditions			
Chills	Additional description: Chills/Shivering events that occurred after 7 days post-vaccination were considered as unsolicited AE.		
subjects affected / exposed	128 / 772 (16.58%)	57 / 761 (7.49%)	
occurrences (all)	130	58	
Injection Site Erythema			
subjects affected / exposed	157 / 772 (20.34%)	85 / 761 (11.17%)	
occurrences (all)	158	85	
Injection Site Induration			
subjects affected / exposed	132 / 772 (17.10%)	64 / 761 (8.41%)	
occurrences (all)	133	64	
Injection Site Pain	Additional description: Pain events that occurred after 7 days post-vaccination were considered as unsolicited AE.		

subjects affected / exposed	350 / 772 (45.34%)	161 / 761 (21.16%)	
occurrences (all)	350	161	
Injection Site Swelling			
subjects affected / exposed	140 / 772 (18.13%)	62 / 761 (8.15%)	
occurrences (all)	140	62	
Malaise	Additional description: Malaise events that occurred after 7 days post-vaccination were considered as unsolicited AE.		
subjects affected / exposed	168 / 772 (21.76%)	90 / 761 (11.83%)	
occurrences (all)	168	90	
Musculoskeletal and connective tissue disorders			
Myalgia	Additional description: Myalgia events that occurred after 7 days post-vaccination were considered as unsolicited AE.		
subjects affected / exposed	206 / 772 (26.68%)	94 / 761 (12.35%)	
occurrences (all)	207	94	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 August 2019	Following changes were made: Table of Study procedures footnote was corrected to indicate that the diary card will be collected at Visit 02 to review any solicited reactions that are still ongoing at Visit 02; Accurately reflected the frequency of reactions at the injection site as presented in the current QIV HD Investigator's Brochure; Eliminated the 3 redundant "≥" symbols in these 3 sentences: "Slovakia recommended vaccination of persons ≥ 59 years of age and older. Malta and Poland recommended vaccination of persons ≥ 55 years of age and older. Three countries (Austria, Belgium, and Ireland) recommended vaccination of those who are ≥ 50 years of age and older"; Provided the correct description of the control vaccine as a subunit vaccine (not a split virion vaccine); Added additional details in the Section 10.5 Reporting SAEs to Health Authorities and IECs/IRBs as per Paul Ehrlich Institute (German Health Authority) request.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported