The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: 114269 (FLU D-QIV-008)

Title: Partially-blind immunogenicity and safety study of GlaxoSmithKline (GSK) Biologicals' seasonal influenza vaccine GSK2321138A in adults.
GSK2321138A (D-QIV): GSK Biologicals' quadrivalent split-virion inactivated seasonal influenza vaccine.

Rationale: The aim of this study was to assess lot-to lot consistency of 3 production lots of D-QIV vaccine, to assess the immunological non-inferiority of D-QIV vaccine compared to TIV-1 (*Fluarix*™) and TIV-2 vaccines for the 3 strains that are included in each of the TIV vaccines, to assess the immunological superiority of D-QIV vaccine compared to TIV-1 (*Fluarix*™) and TIV-2 vaccines for the B strain that is not included in each of the TIV vaccine and to evaluate the immunogenicity and safety of D-QIV and TIV vaccines when administered as a single dose to subjects 18 years and older.
Fluarix™ (TIV-1): GSK Biologicals' trivalent split-virion inactivated seasonal influenza vaccine containing the recommended World Health Organisation (WHO) strains for the Northern Hemisphere 2010-2011 season.
GSK2604409A (TIV-2): GSK Biologicals' trivalent split-virion inactivated seasonal influenza vaccine containing an alternate B lineage strain from the Yamagata lineage not represented in the Northern Hemisphere 2010-2011 season recommendation.

Phase: III

Study Period: 04 October 2010 to 06 June 2011

Study Design: Partially-blind*, randomized (5:5:5:5:3), controlled, multi-centre, multi-country study with 5 parallel groups.
* 4 groups were double-blinded throughout the study period up to Day 180 and 1 group was open (for details, please refer to the treatment section).

Centres: 43 Centres (13 centres in Germany, 4 centres in Korea, 9 centres in Romania, 5 centres in Spain, 2 centres in Taiwan and 10 centres in United States).
Note: There were concerns regarding the integrity of study data from a single study site in Romania which enrolled 102 subjects in the study. At the time the concerns arose, the analyses for the study already had been completed. Because evaluation of data from this site did not reveal irregularities when compared with overall study data and because GSK had no current plans to use the data from the study in support of any regulatory filings, data from this site were not excluded from the analyses reflected in this document.

Indication: Immunisation of adults 18 years of age and older against seasonal influenza infection.

Treatment: The treatment groups were as follows:

- D-QIV 1 Group: subjects received 1 dose of D-QIV Lot 1 vaccine.
- D-QIV 2 Group: subjects received 1 dose of D-QIV Lot 2 vaccine.
- D-QIV 3 Group: subjects received 1 dose of D-QIV Lot 3 vaccine.
- TIV-1 Group: subjects received 1 dose of TIV-1 vaccine.
- TIV-2 Group: subjects received 1 dose of TIV-2 vaccine.

All vaccines were administered as a single dose intramuscularly in the deltoid region of the non-dominant arm at Day 0.
Groups D-QIV 1, 2, 3 and TIV-1 were double-blinded throughout the study period up to Day 180.
The TIV-2 Group was open and subjects from this group were followed until Day 21 only, after which their participation in the study was complete.

Objectives:

- To assess the lot-to-lot consistency of 3 lots of D-QIV vaccine in terms of haemagglutination inhibition (HI) antibody geometric mean titres (GMTs)

Criterion to evaluate lot-to-lot consistency:

- Lot-to-lot consistency was reached if, for each vaccine strain, the limits of the 2-sided 95% confidence interval (CI) for the largest geometric mean ratio (GMR) among the 3 lots were in between 0.67 and 1.5.

- To assess the immunological non-inferiority (in terms of HI antibody GMTs and seroconversion rates$ (SCRs)) of the D-QIV vaccine compared to TIV-1 and TIV-2 vaccines for the 3 strains that were included in each of TIV-1 and TIV-2 vaccines.

Criteria to conclude non-inferiority:
Non-inferiority in terms of GMTs and SCR was reached

- if the upper limit of the 2-sided 95% CI for the ratio of GMT of TIV-1 vaccine or TIV-2 vaccine over D-QIV vaccine did not exceed 1.5 for each strain that was included in the TIV-1 and TIV-2 vaccines respectively.
- and if the upper limit of the 2-sided asymptotic standardised 95% CI for the difference in SCR (TIV-1 vaccine or TIV-2 vaccine minus D-QIV vaccine) did not exceed 10% for each strain that was included in the TIV-1 and

TIV-2 vaccines respectively.

- To assess the immunological superiority (in terms of HI antibody GMTs and SCRs)) of the D-QIV vaccine compared to TIV-1 and TIV-2 vaccines for the B strain that was not included in each TIV vaccine.

Criterion to conclude superiority:

- Immunologic superiority of the unique B strain in D-QIV vaccine was demonstrated if the lower limit of the 2-sided 95% CI on GMT ratio (D-QIV vaccine over TIV-1 vaccine or D-QIV vaccine over TIV-2 vaccine) were >1 and the lower limit of the 2-sided 95%CI for the difference in SCR (D-QIV vaccine minus TIV-1 vaccine or TIV-2 vaccine) were > 0.

$Please refer to the next section for SCR definition.

Primary Outcome/Efficacy Variable:

- Humoral immune response in terms of HI antibodies
  - Serum HI antibody titres against the 4 influenza vaccine strains were used to calculate:
    - GMTs at Day 0 and Day 21
    - SCRs* at Day 21

*SCR is defined as the percentage of vaccinees who have either a pre-vaccination titre < 1:10 and a post-vaccination titre ≥ 1:40 or a pre-vaccination titre ≥ 1:10 and at least a 4-fold increase in post-vaccination titre.

Secondary Outcome/Efficacy Variable(s):

Immunogenicity:

- Humoral immune response in terms of HI antibodies
  - Serum HI antibody titres against the 4 influenza vaccine strains were used to calculate:
    - Seropositivity rates on Days 0 and 21.
    - GMTs of HI antibody titres on Days 0 and 21.
    - SCR on Day 21
    - Mean Geometric Increase** (MGI) on Day 21
    - Seroprotection rate*** (SPR) on Days 0 and 21

**MGI is defined as the geometric mean of the within subject ratios of the post-vaccination reciprocal HI titre to the Day 0 reciprocal HI titre.

***SPR is defined as the percentage of vaccinees with a serum HI titre ≥1:40 that usually is accepted as indicating protection.

Safety:

- Solicited local adverse events (AEs)
  - Occurrence, duration and intensity during a 7-day follow-up period (i.e. day of vaccination and 6 subsequent days) after the vaccination in each group.
- Solicited general AEs
  - Occurrence, duration, intensity and relationship to vaccination during a 7-day follow-up period (i.e. day of vaccination and 6 subsequent days) after the vaccination in each group.
- Unsolicited AEs
  - Occurrence, intensity and relationship to vaccination during a 21-day follow-up period (i.e. day of vaccination and 20 subsequent days) after the vaccination in each group.
- Serious adverse events (SAEs), AEs with medically attended events (MAE)¥ and potential immune-mediated diseases (pIMD)$.
  - Occurrence and relationship to vaccination during the entire study period in each group.

¥ MAEs refer to non-serious and serious events leading to an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. If a medically-attended adverse event was leading to hospitalisation (or met any other SAE criterion), it was reported as SAE.

$ pIMDs are a subset of AEs that include both clearly autoimmune diseases and also other inflammatory and/or neurologic disorders which may or may not have an autoimmune etiology.

Statistical Methods:

The analyses were performed on the Total Vaccinated cohort and the According-To-Protocol (ATP) cohort for immunogenicity.

- The Total Vaccinated cohort included all vaccinated subjects.
- The ATP cohort for immunogenicity included all vaccinated and eligible subjects (i.e. those meeting all eligibility criteria, complying with the protocol procedures and with no elimination criteria assigned during the study) for whom data concerning immunogenicity outcome measures were available. These included subjects for whom assay results were available for antibodies against at least 1 study vaccine antigen component after vaccination.

Analysis of immunogenicity:
The analysis for immunogenicity was performed on the ATP cohort for immunogenicity.
To assess the lot-to-lot consistency in terms of GMTs of 3 lots of D-QIV vaccines, the adjusted GMT ratio at post-vaccination (Day 21) between D-QIV groups for each strain was computed by fitting an ANCOVA model including the pre-vaccination concentration as covariate: for each virus strain, the largest pairwise GMT ratio among the 3 D-QIV groups, taken 2 at a time, was checked against the criteria for evaluation.
To evaluate the non-inferiority and the superiority of the D-QIV vaccine compared to TIV-1 and TIV-2 vaccines respectively for the common strains in the D-QIV and the TIVs and for the additional B strain not included in the TIVs, the adjusted GMT ratio and the SCR difference with their 2-sided 95% confidence interval were computed for the comparison of interest.

Moreover, for each strain the following parameters were calculated by group (D-QIV, TIV-1 and TIV-2) with 95% CI:

- Seropositivity rates and GMTs at Day 0 and at Day 21
- SCRs at Day 21
- SPRs at Day 0 and Day 21
- MGIs at Day 21

Analysis of safety:
The analysis for safety was performed on the Total Vaccinated cohort.
The percentages of subjects reporting each individual solicited local and general symptoms during the 7-day (Days 0-6) follow-up period after vaccine were tabulated with exact 95% CIs for groups D-QIV, TIV-1 and TIV-2. The same tabulation was performed for grade 3 symptoms and for general symptom assessed by the investigator as causally related to vaccination.
Moreover, descriptive statistics (Mean and Median) of the duration with local and general symptoms were tabulated.
The percentage of subjects with at least 1 report of an unsolicited AE classified by Medical Dictionary for Regulatory Activities (MedDRA) preferred terms during a 21-day follow-up period (i.e. day of vaccination and 20 subsequent days) was tabulated for groups D-QIV, TIV-1 and TIV-2. The same tabulation was performed for grade 3 unsolicited AEs and for AEs assessed by the investigators as causally related to vaccination.
The occurrences of MAEs, pIMDs and SAEs reported during the entire study period (Day 0 - Day 180) were tabulated according to MedDRA preferred terms.

Study Population: Healthy, or with stable underlying medical conditions, male or female subjects 18 years and older at the time of the first vaccination without prior receipt of any influenza vaccine within 6 months preceding the first dose of study vaccine were included in the study. Female subjects were to be of non-childbearing potential or if of childbearing potential, had to practice adequate contraception for 30 days prior to vaccination, to have a negative pregnancy test on the day of vaccination, and were to continue such precautions for 2 months after completion of the vaccination. Written informed consent was obtained from the subject prior to enrolment.

Number of subjects	**D-QIV Group**	**TIV-1 Group**	**TIV-2 Group**
Planned, N	3000	1000	600
Randomised, N (Total Vaccinated cohort)	3036	1010	610
Completed to Day 21, n (%)	Not Applicable	Not Applicable	606 (99.3)
Completed to Day 180, n (%)	2994 (98.6)*	997 (98.7)	Not Applicable
Total Number Subjects Withdrawn, n (%)	40 (1.3)	13 (1.3)	4 (0.7)
Withdrawn due to Adverse Events n (%)	10 (0.3)	3 (0.3)	1 (0.2)
Withdrawn due to Lack of Efficacy n (%)	Not Applicable	Not Applicable	Not Applicable
Withdrawn for other reasons n (%)	30 (1.0)	10 (1.0)	3 (0.5)
Demographics	**D-QIV Group**	**TIV-1 Group**	**TIV-2 Group**
N (Total Vaccinated cohort)	3036	1010	610
Females:Males, n(%)	1745(57.5):1291(42.5)	548 (54.3):462(45.7)	343(56.2):267(43.8)
Mean Age, years (SD)	57.9 (17.70)	58.1 (17.83)	58.1 (17.92)
White - Caucasian / European heritage, n (%)	2078 (68.4)	699 (69.2)	414 (67.9)

*2 subjects had unknown completion status at the time of writing the CTRS.

Primary Efficacy Results: Adjusted GMT ratios of HI antibody at Day 21 for the maximum difference between 2 lots of D-QIV for A/California/7/2009 (H1N1) (ATP cohort for immunogenicity)

				Adjusted GMT ratio (D-QIV-1 Group /D-QIV-2 Group*)		
D-QIV-1 Group		**D-QIV-2 Group**			**95% CI**	
N	**Adjusted GMT**	**N**	**Adjusted GMT**	**Value**	**LL**	**UL**

600	196.5	599	209.0	0.94	0.80	1.10

Adjusted GMT = geometric mean antibody titre adjusted for baseline titre
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMT ratio ; LL = lower limit, UL = upper limit
*This was the maximum difference among 3 pairwise comparisons of 2 lots
Lot-to-lot consistency criterion: limits of the 2-sided 95% CI for the largest GMT Ratio among the 3 lots between 0.67 and 1.5.

Primary Efficacy Results: Adjusted GMT ratios of HI antibody at Day 21 for the maximum difference between 2 lots of D-QIV for A/Victoria/210/2009 (H3N2) (ATP cohort for immunogenicity)

				Adjusted GMT ratio (D-QIV-1 Group /D-QIV-2 Group*)		
D-QIV-1 Group		**D-QIV-2 Group**			**95% CI**	
N	**Adjusted GMT**	**N**	**Adjusted GMT**	**Value**	**LL**	**UL**
600	306.8	599	330.6	0.93	0.81	1.06

Adjusted GMT = geometric mean antibody titre adjusted for baseline titre
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMT ratio; LL = lower limit, UL = upper limit
*This was the maximum difference among 3 pairwise comparisons of 2 lots
Lot-to-lot consistency criterion: limits of the 2-sided 95% CI for the largest GMT Ratio among the 3 lots between 0.67 and 1.5.

Primary Efficacy Results: Adjusted GMT ratios of HI antibody at Day 21 for the maximum difference between 2 lots of D-QIV for B/Brisbane/60/2008 (Victoria lineage) (ATP cohort for immunogenicity)

				Adjusted GMT ratio (D-QIV-1 Group /D-QIV-2 Group *)		
D-QIV-1 Group		**D-QIV-2 Group**			**95% CI**	
N	**Adjusted GMT**	**N**	**Adjusted GMT**	**Value**	**LL**	**UL**
600	410.7	599	396.7	1.04	0.93	1.15

Adjusted GMT = geometric mean antibody titre adjusted for baseline titre
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMT ratio
*This was the maximum difference among 3 pairwise comparisons of 2 lots
Lot-to-lot consistency criterion: limits of the 2-sided 95% CI for the largest GMT Ratio among the 3 lots between 0.67 and 1.5.

Primary Efficacy Results: Adjusted GMT ratios of HI antibody at Day 21 for the maximum difference between 2 lots of D-QIV for B/Brisbane/3/2007 (Yamagata) (ATP cohort for immunogenicity)

				Adjusted GMT ratio (D-QIV-1 Group /D-QIV-2 Group*)		
D-QIV-1 Group		**D-QIV-2 Group**			**95% CI**	
N	**Adjusted GMT**	**N**	**Adjusted GMT**	**Value**	**LL**	**UL**
600	605.0	599	599.0	1.01	0.90	1.13

Adjusted GMT = geometric mean antibody titre adjusted for baseline titre
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMT ratio); LL = lower limit, UL = upper limit
*This was the maximum difference among 3 pairwise comparisons of 2 lots
Lot-to-lot consistency criterion: limits of the 2-sided 95% CI for the largest GMT Ratio among the 3 lots between 0.67 and 1.5.

Primary Efficacy Results: Non inferiority of D-QIV versus TIV (TIV-1 & TIV-2) in terms of GMTs (adjusted GMT ratio) at Day 21 for the 2 A-strains (ATP cohort for immunogenicity)

					Adjusted GMT ratio (TIV Group / D-QIV Group)		
	TIV Group		**D-QIV Group**			**95% CI**	
Antibody	**N**	**Adjusted GMT**	**N**	**Adjusted GMT**	**Value**	**LL**	**UL**
A/California/7/2009 (H1N1)	1135	214.8	1801	201.6	1.07	0.96	1.18
A/Victoria/210/2009 (H3N2)	1135	312.2	1801	318.5	0.98	0.90	1.07

Adjusted GMT = geometric mean antibody titre adjusted for baseline titre
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMT ratio ; LL = lower limit, UL = upper limit
Non-inferiority criterion: UL of the 2-sided 95% CI for the ratio of GMT of TIV Group over D-QIV Group ≤ 1.5

Primary Efficacy Results: Non inferiority of D-QIV versus TIV (TIV-1 & TIV-2) in terms of SCR (difference in vaccine response rate) at Day 21 for the 2 A-strains (ATP cohort for immunogenicity)

								Difference in SCR (TIV Group minus D-QIV Group)		
		TIV Group			D-QIV Group				95% CI	
Antibody	**Pre-vaccination status**	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
A/California/7/2009 (H1N1)	Total	1135	892	78.6	1801	1396	77.5	1.08	-2.03	4.11
A/Victoria/210/2009 (H3N2)	Total	1135	769	67.8	1801	1287	71.5	-3.71	-7.15	-0.30

SCR defined as :
- For initially seronegative subjects : post-vaccination antibody titre ≥ 1:40 at post-vaccination
- For initially seropositive subjects : antibody titre at post-vaccination ≥ 4 fold the pre-vaccination antibody titre

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of seroconverted subjects
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit
Non-inferiority criterion: UL of the 2-sided 95% CI for the difference in SCR (TIV Group minus D-QIV Group) ≤ 10%.

Primary Efficacy Results: Non inferiority of D-QIV versus TIV-1 in terms of GMTs (adjusted GMT ratio) at Day 21 for the B/Brisbane/60/2008 (Victoria lineage) strain (ATP cohort for immunogenicity)

				Adjusted GMT ratio (TIV-1 Group / D-QIV Group)		
TIV-1 Group		**D-QIV Group**			**95% CI**	
N	**Adjusted GMT**	**N**	**Adjusted GMT**	**Value**	**LL**	**UL**
605	395.3	1801	404.2	0.98	0.90	1.07

Adjusted GMT = geometric mean antibody titre adjusted for baseline titre
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMT ratio ; LL = lower limit, UL = upper limit
Non-inferiority criterion: UL of the 2-sided 95% CI for the ratio of GMT of TIV-1 Group over D-QIV Group ≤ 1.5

Primary Efficacy Results: Non inferiority of D-QIV versus TIV-1 in terms of SCR (difference in vaccine response rate) at Day 21 for the B/Brisbane/60/2008 (Victoria lineage) strain (ATP cohort for immunogenicity)

								Difference in SCR (TIV-1 Group minus D-QIV Group)		
		TIV-1 Group			D-QIV Group				95% CI	
Antibody	**Pre-vaccination status**	**N**	**N**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
B/Brisbane/60/2008 (Victoria)	Total	605	335	55.4	1801	1046	58.1	-2.71	-7.29	1.83

SCR defined as :
- For initially seronegative subjects : post-vaccination antibody titre ≥ 1:40 at post-vaccination
- For initially seropositive subjects : antibody titre at post-vaccination ≥ 4 fold the pre-vaccination antibody titre

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of seroconverted subjects
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit
Non-inferiority criterion: UL of the 2-sided 95% CI for the difference in SCR (TIV-1 Group minus D-QIV Group) ≤ 10%.

Primary Efficacy Results: Non inferiority of D-QIV versus TIV-2 in terms of GMTs (adjusted GMT ratio) at Day 21 for the B/Brisbane/3/2007 (Yamagata lineage) strain (ATP cohort for immunogenicity)

				Adjusted GMT ratio (TIV-2 Group / D-QIV Group)		
TIV-2 Group		**D-QIV Group**			**95% CI**	
N	**Adjusted GMT**	**N**	**Adjusted GMT**	**Value**	**LL**	**UL**
530	584.7	1801	600.8	0.97	0.89	1.07

Adjusted GMT = geometric mean antibody titre adjusted for baseline titre
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMT ratio ; LL = lower limit, UL = upper limit
Non-inferiority criterion: UL of the 2-sided 95% CI for the ratio of GMT of TIV-2 Group over D-QIV Group ≤ 1.5

Primary Efficacy Results: Non inferiority of D-QIV versus TIV-2 in terms of SCR (difference in vaccine response rate) at Day 21 for the B/Brisbane/3/2007 (Yamagata lineage) strain (ATP cohort for immunogenicity)

		Difference in SCR (TIV-2 Group minus D-QIV Group)

		TIV-2 Group			D-QIV Group				95% CI	
Antibody	**Pre-vaccination status**	**N**	**N**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
B/Brisbane/3/2007 (Yamagata)	Total	530	313	59.1	1801	1112	61.7	-2.69	-7.47	2.01

SCR defined as :
- For initially seronegative subjects : post-vaccination antibody titre ≥ 1:40 at post-vaccination
- For initially seropositive subjects : antibody titre at post-vaccination ≥ 4 fold the pre-vaccination antibody titre

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of seroconverted subjects
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit
Non-inferiority criterion: UL of the 2-sided 95% CI for the difference in SCR (TIV-2 Group minus D-QIV Group) ≤ 10%.

Primary Efficacy Results: Superiority of D-QIV versus TIV-2 in terms of GMTs (adjusted GMT ratio) at Day 21 for the B/Brisbane/60/2008 (Victoria lineage) strain (ATP cohort for immunogenicity)

				Adjusted GMT ratio (D-QIV Group / TIV-2 Group)		
D-QIV Group		**TIV-2 Group**			**95% CI**	
N	**Adjusted GMT**	**N**	**Adjusted GMT**	**Value**	**LL**	**UL**
1801	403.5	530	259.4	1.56	1.42	1.70

Adjusted GMT = geometric mean antibody titre adjusted for baseline titre
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMT ratio ; LL = lower limit, UL = upper limit
Superiority criterion: LL of the 2-sided 95% CI on GMT ratio (D-QIV Group /TIV-2 Group) >1.

Primary Efficacy Results: Superiority of D-QIV versus TIV-2 in terms of SCR (difference in vaccine response rate) at Day 21 for the B/Brisbane/60/2008 (Victoria lineage) strain (ATP cohort for immunogenicity)

								Difference in SCR (D-QIV Group minus TIV-2 Group)		
		TIV-2 Group			**D-QIV Group**				**95% CI**	
Antibody	**Pre-vaccination status**	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
B/Brisbane/60/2008 (Victoria)	Total	530	252	47.5	1801	1046	58.1	10.53	5.70	15.33

SCR defined as :
- For initially seronegative subjects : post-vaccination antibody titre ≥ 1:40 at post-vaccination
- For initially seropositive subjects : antibody titre at post-vaccination ≥ 4 fold the pre-vaccination antibody titre

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of seroconverted subjects
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit
Superiority criterion: LL of the 2-sided 95% CI for the difference in SCR (D-QIV Group minus TIV-2 Group) > 0.

Primary Efficacy Results: Superiority of D-QIV versus TIV-1 in terms of GMTs (adjusted GMT ratio) at Day 21 for the B/Brisbane/3/2007 (Yamagata lineage) strain (ATP cohort for immunogenicity)

				Adjusted GMT ratio (D-QIV Group / TIV-1 Group)		
D-QIV Group		**TIV-1 Group**			**95% CI**	
N	**Adjusted GMT**	**N**	**Adjusted GMT**	**Value**	**LL**	**UL**
1801	601.2	605	387.7	1.55	1.41	1.70

Adjusted GMT = geometric mean antibody titre adjusted for baseline titre
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMT ratio ; LL = lower limit, UL = upper limit
Superiority criterion: LL of the 2-sided 95% CI on GMT ratio (D-QIV Group /TIV-1 Group) >1.

Primary Efficacy Results: Superiority of D-QIV versus TIV-1 in terms of SCR (difference in vaccine response rate) at Day 21 for the B/Brisbane/3/2007 (Yamagata lineage) strain (ATP cohort for immunogenicity)

								Difference in SCR (D-QIV Group minus TIV-1 Group)		
		TIV-1 Group			**D-QIV Group**				**95% CI**	
Antibody	**Pre-vaccination status**	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**

B/Brisbane/3/2007 (Yamagata) (	Total	605	276	45.6	1801	1112	61.7	16.12	11.54	20.65

SCR defined as :
- For initially seronegative subjects : post-vaccination antibody titre ≥ 1:40 at post-vaccination
- For initially seropositive subjects : antibody titre at post-vaccination ≥ 4 fold the pre-vaccination antibody titre

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of seroconverted subjects
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit
Superiority criterion: LL of the 2-sided 95% CI for the difference in SCR (D-QIV Group minus TIV-1 Group) > 0.

Primary Efficacy Results: Seropositivity rates and GMTs for HI antibodies at Day 0 and Day 21 (ATP cohort for immunogenicity)

Antibody	Group	Timing	N	≥ 1:10				GMT*		
				n	%	95% CI		value	95% CI	
						LL	UL		LL	UL
A/California/7/2009 (H1N1)	D-QIV	PRE	1801	967	53.7	51.4	56.0	14.7	13.8	15.6
		PI(D21)	1809	1738	96.1	95.1	96.9	201.1	188.1	215.1
	TIV-1	PRE	605	352	58.2	54.1	62.1	15.6	14.1	17.3
		PI(D21)	608	586	96.4	94.6	97.7	218.4	194.2	245.6
	TIV-2	PRE	530	291	54.9	50.6	59.2	14.4	12.9	16.0
		PI(D21)	534	514	96.3	94.3	97.7	213.0	187.6	241.9
A/Victoria/210/2009 (H3N2)	D-QIV	PRE	1801	1416	78.6	76.7	80.5	34.0	31.8	36.3
		PI(D21)	1809	1783	98.6	97.9	99.1	314.7	296.8	333.6
	TIV-1	PRE	605	488	80.7	77.3	83.7	38.1	34.1	42.7
		PI(D21)	608	594	97.7	96.2	98.7	298.2	268.4	331.3
	TIV-2	PRE	530	425	80.2	76.5	83.5	35.7	31.6	40.3
		PI(D21)	534	528	98.9	97.6	99.6	340.4	304.3	380.9
B/Brisbane/60/2008 (Victoria)	D-QIV	PRE	1801	1541	85.6	83.9	87.2	73.8	69.1	78.8
		PI(D21)	1809	1795	99.2	98.7	99.6	404.6	386.6	423.4
	TIV-1	PRE	605	511	84.5	81.3	87.3	73.6	65.5	82.8
		PI(D21)	608	601	98.8	97.6	99.5	393.8	362.7	427.6
	TIV-2	PRE	530	452	85.3	82.0	88.2	71.7	63.4	81.0
		PI(D21)	534	518	97.0	95.2	98.3	258.5	234.6	284.8
B/Brisbane/3/2007 (Yamagata)	D-QIV	PRE	1801	1554	86.3	84.6	87.8	101.4	94.5	108.8
		PI(D21)	1809	1794	99.2	98.6	99.5	601.8	573.3	631.6
	TIV-1	PRE	605	525	86.8	83.8	89.4	100.9	89.3	113.9
		PI(D21)	608	597	98.2	96.8	99.1	386.6	351.5	425.3
	TIV-2	PRE	530	457	86.2	83.0	89.0	99.8	87.7	113.5
		PI(D21)	534	532	99.6	98.7	100	582.5	534.6	634.7

GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE= Pre-vaccination Dose 1 Blood sample at Day 0
PI(D21)= Post-vaccination Dose 1 Blood sample at Day 21
* Primary outcome variable

Primary Efficacy Results: SCR for HI antibodies at Day 21 (ATP cohort for immunogenicity)

Antibody	Group	N	SCR			
			n	%	95% CI	
					LL	UL
A/California/7/2009 (H1N1)	D-QIV	1801	1396	77.5	75.5	79.4
	TIV-1	605	467	77.2	73.6	80.5
	TIV-2	530	425	80.2	76.5	83.5
A/Victoria/210/2009 (H3N2)	D-QIV	1801	1287	71.5	69.3	73.5
	TIV-1	605	398	65.8	61.9	69.6
	TIV-2	530	371	70.0	65.9	73.9
B/Brisbane/60/2008 (Victoria)	D-QIV	1801	1046	58.1	55.8	60.4

	TIV-1	605	335	55.4	51.3	59.4
	TIV-2	530	252	47.5	43.2	51.9
B/Brisbane/3/2007 (Yamagata)	D-QIV	1801	1112	61.7	59.5	64.0
	TIV-1	605	276	45.6	41.6	49.7
	TIV-2	530	313	59.1	54.7	63.3

Seroconversion defined as:
- For initially seronegative subjects, antibody titre ≥ 1:40 after vaccination
- For initially seropositive subjects, antibody titre after vaccination ≥ 4 fold the pre-vaccination antibody titre
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of seroconverted subjects
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Secondary Outcome Variable(s): Seroprotection rates for HI antibodies at Day 0 and Day 21 (ATP cohort for immunogenicity)

Antibody	**Group**	**Timing**	**N**	**SPR**			
				n	**%**	**95% CI**	
						LL	**UL**
A/California/7/2009 (H1N1)	D-QIV	PRE	1801	514	28.5	26.5	30.7
		PI(D21)	1809	1651	91.3	89.9	92.5
	TIV-1	PRE	605	167	27.6	24.1	31.4
		PI(D21)	608	558	91.8	89.3	93.8
	TIV-2	PRE	530	139	26.2	22.5	30.2
		PI(D21)	534	495	92.7	90.2	94.8
A/Victoria/210/2009 (H3N2)	D-QIV	PRE	1801	965	53.6	51.2	55.9
		PI(D21)	1809	1751	96.8	95.9	97.6
	TIV-1	PRE	605	353	58.3	54.3	62.3
		PI(D21)	608	583	95.9	94.0	97.3
	TIV-2	PRE	530	285	53.8	49.4	58.1
		PI(D21)	534	517	96.8	95.0	98.1
B/Brisbane/60/2008 (Victoria)	D-QIV	PRE	1801	1423	79.0	77.1	80.9
		PI(D21)	1809	1788	98.8	98.2	99.3
	TIV-1	PRE	605	477	78.8	75.4	82.0
		PI(D21)	608	599	98.5	97.2	99.3
	TIV-2	PRE	530	412	77.7	74.0	81.2
		PI(D21)	534	513	96.1	94.1	97.5
B/Brisbane/3/2007 (Yamagata)	D-QIV	PRE	1801	1494	83.0	81.1	84.7
		PI(D21)	1809	1792	99.1	98.5	99.5
	TIV-1	PRE	605	497	82.1	78.9	85.1
		PI(D21)	608	595	97.9	96.4	98.9
	TIV-2	PRE	530	441	83.2	79.7	86.3
		PI(D21)	534	532	99.6	98.7	100

N = number of subjects with available results
n/% = number/percentage of seroprotected subjects (HI titre ≥ 1:40)
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination Dose 1 Blood sample at Day 0
PI(D21)= Post-vaccination Dose 1 Blood sample at Day 21

Secondary Outcome Variable(s): Mean geometric increase (MGI) for HI antibodies at Day 21 (ATP cohort for immunogenicity)

Antibody	**Group**	**N**	**MGI**		
			Value	**95% CI**	
				LL	**UL**
A/California/7/2009 (H1N1)	D-QIV	1801	13.69	12.70	14.76
	TIV-1	605	13.92	12.23	15.84
	TIV-2	530	14.88	12.91	17.16
A/Victoria/210/2009 (H3N2)	D-QIV	1801	9.28	8.64	9.96
	TIV-1	605	7.84	6.93	8.88
	TIV-2	530	9.52	8.33	10.89

B/Brisbane/60/2008 (Victoria)	D-QIV	1801	5.48	5.12	5.85
	TIV-1	605	5.37	4.75	6.06
	TIV-2	530	3.60	3.25	3.98
B/Brisbane/3/2007 (Yamagata)	D-QIV	1801	5.93	5.53	6.36
	TIV-1	605	3.84	3.42	4.30
	TIV-2	530	5.84	5.13	6.65

N = number of subjects with pre- and post-vaccination results available
MGI = Geometric mean of the within -subject ratios of the post-vaccination reciprocal HI titre to the Day 0 reciprocal HI titre
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Secondary Outcome Variable(s): Number/percentage of subjects with solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated cohort)

Symptom	**Intensity**	**D-QIV Group**					**TIV-1 Group**					**TIV-2 Group**				
					95 % CI					**95 % CI**					**95 % CI**	
		N	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Pain	Any	3015	1096	36.4	34.6	38.1	1003	369	36.8	33.8	39.9	607	190	31.3	27.6	35.2
	Grade 3	3015	24	0.8	0.5	1.2	1003	12	1.2	0.6	2.1	607	3	0.5	0.1	1.4
Redness	Any	3015	58	1.9	1.5	2.5	1003	17	1.7	1.0	2.7	607	12	2.0	1.0	3.4
	> 100 mm	3015	1	0.0	0.0	0.2	1003	0	0.0	0.0	0.4	607	0	0.0	0.0	0.6
Swelling	Any	3015	62	2.1	1.6	2.6	1003	21	2.1	1.3	3.2	607	8	1.3	0.6	2.6
	> 100 mm	3015	0	0.0	0.0	0.1	1003	0	0.0	0.0	0.4	607	0	0.0	0.0	0.6

N= number of subjects with the documented dose
n/%= number/percentage of subjects reporting the symptom at least once
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
Any = occurrence of any solicited local symptoms regardless of intensity grade
Grade 3 pain = significant pain at rest/pain that prevented normal every day activities.

Secondary Outcome Variable(s): Number of days with local symptoms during the 7-day post-vaccination period (Total Vaccinated cohort)

Solicited symptom	**Group**	**N**	**Mean**	**Median**
Pain	D-QIV	1096	2.1	2.0
	TIV-1	369	2.1	2.0
	TIV-2	190	2.0	2.0
Redness	D-QIV	58	2.4	2.0
	TIV-1	17	1.9	1.0
	TIV-2	12	2.3	1.0
Swelling	D-QIV	62	2.4	2.0
	TIV-1	21	2.0	2.0
	TIV-2	8	2.6	2.5

N = Number of subjects with the symptom and without the missing confirmed grade

Secondary Outcome Variable(s): Number/percentage of subjects with solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated cohort)

Symptom	**Intensity/ Relationship**	**D-QIV Group**					**TIV-1 Group**					**TIV-2 Group**				
					95 % CI					**95 % CI**					**95 % CI**	
		N	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Fatigue	Any	3011	477	15.8	14.6	17.2	1003	185	18.4	16.1	21.0	607	90	14.8	12.1	17.9
	Grade 3	3011	21	0.7	0.4	1.1	1003	6	0.6	0.2	1.3	607	3	0.5	0.1	1.4
	Related	3011	334	11.1	10.0	12.3	1003	132	13.2	11.1	15.4	607	64	10.5	8.2	13.3
Gastrointestinal	Any	3011	197	6.5	5.7	7.5	1003	65	6.5	5.0	8.2	607	36	5.9	4.2	8.1
	Grade 3	3011	11	0.4	0.2	0.7	1003	2	0.2	0.0	0.7	607	2	0.3	0.0	1.2
	Related	3011	109	3.6	3.0	4.4	1003	35	3.5	2.4	4.8	607	19	3.1	1.9	4.8
Headache	Any	3011	480	15.9	14.7	17.3	1003	164	16.4	14.1	18.8	607	80	13.2	10.6	16.1
	Grade 3	3011	26	0.9	0.6	1.3	1003	8	0.8	0.3	1.6	607	4	0.7	0.2	1.7
	Related	3011	277	9.2	8.2	10.3	1003	97	9.7	7.9	11.7	607	48	7.9	5.9	10.3
Joint pain at other location	Any	3011	254	8.4	7.5	9.5	1003	104	10.4	8.6	12.4	607	57	9.4	7.2	12.0
	Grade 3	3011	14	0.5	0.3	0.8	1003	7	0.7	0.3	1.4	607	2	0.3	0.0	1.2
	Related	3011	172	5.7	4.9	6.6	1003	61	6.1	4.7	7.7	607	29	4.8	3.2	6.8
Muscle	Any	3011	493	16.4	15.1	17.7	1003	195	19.4	17.0	22.0	607	98	16.1	13.3	19.3

aches	Grade 3	3011	14	0.5	0.3	0.8	1003	8	0.8	0.3	1.6	607	3	0.5	0.1	1.4
	Related	3011	356	11.8	10.7	13.0	1003	137	13.7	11.6	15.9	607	61	10.0	7.8	12.7
Shivering	Any	3011	125	4.2	3.5	4.9	1003	50	5.0	3.7	6.5	607	26	4.3	2.8	6.2
	Grade 3	3011	11	0.4	0.2	0.7	1003	3	0.3	0.1	0.9	607	1	0.2	0.0	0.9
	Related	3011	82	2.7	2.2	3.4	1003	30	3.0	2.0	4.2	607	19	3.1	1.9	4.8
Temperature (Axillary)	≥ 37.5°C	3011	48	1.6	1.2	2.1	1003	12	1.2	0.6	2.1	607	9	1.5	0.7	2.8
	>39.0°C	3011	0	0.0	0.0	0.1	1003	0	0.0	0.0	0.4	607	0	0.0	0.0	0.6
	Related	3011	30	1.0	0.7	1.4	1003	5	0.5	0.2	1.2	607	6	1.0	0.4	2.1

N= number of subjects with the documented dose
n/%= number/percentage of subjects reporting the symptom at least once
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
Any = occurrence of any solicited general symptoms regardless of intensity grade or relationship to vaccination
Grade 3 symptoms = symptoms which prevented normal every day activities
Related = general symptoms assessed by the investigator as causally related to the study vaccination

Secondary Outcome Variable(s): Number of days with general symptoms during the 7-day post-vaccination period (Total Vaccinated cohort)

Solicited symptom	**Group**	**N**	**Mean**	**Median**
Fatigue	D-QIV	477	2.4	2.0
	TIV-1	185	2.4	2.0
	TIV-2	90	2.4	2.0
Gastrointestinal	D-QIV	197	2.3	2.0
	TIV-1	65	2.2	2.0
	TIV-2	36	2.3	2.0
Headache	D-QIV	480	2.1	2.0
	TIV-1	164	2.1	2.0
	TIV-2	80	2.1	1.0
Joint pain at other location	D-QIV	254	2.8	2.0
	TIV-1	104	2.7	2.0
	TIV-2	57	2.8	2.0
Muscle aches	D-QIV	493	2.4	2.0
	TIV-1	195	2.3	2.0
	TIV-2	98	2.2	2.0
Shivering	D-QIV	125	2.1	2.0
	TIV-1	50	1.7	1.0
	TIV-2	26	1.9	1.5
Temperature	D-QIV	48	1.8	1.0
	TIV-1	12	1.5	1.0
	TIV-2	9	2.2	2.0

N = Number of subjects with the symptom and without the missing confirmed grade

Secondary Outcome Variable(s): Percentage of subjects reporting the occurrence of pIMDs* during the entire study period (Total Vaccinated cohort)

pIMDs	**D-QIV Group N = 3036**	**TIV-1 Group N = 1010**	**TIV-2 Group N = 610**
Subjects with any pIMD(s), n (%)	1 (0.0)	1 (0.1)	0 (0.0)
Subjects with related pIMD(s), n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple sclerosis	1 (0.0)	-	-
VIIth nerve paralysis	-	1 (0.1)	-

-= pIMD absent
Related= pIMD assessed by the investigator as causally related to the study vaccination
* the 3 D-QIV groups and the TIV-1 group were followed approximately 180 days, the TIV-2 group followed until Day 21

Secondary Outcome Variable(s): Percentage of subjects reporting unsolicited AE with medically attended visit (MAEs*) during the entire study period (Total Vaccinated cohort)

MAE(s)	**D-QIV Group N = 3036**	**TIV-1 Group N = 1010**	**TIV-2 Group N = 610**
Subjects with any MAE(s), n (%)	688 (22.7)	216 (21.4)	52 (8.5)
Subjects with related MAE(s), n (%)	11 (0.4)	4 (0.4)	5 (0.8)

Nasopharyngitis	64 (2.1)	23 (2.3)	5 (0.8)
Bronchitis	48 (1.6)	9 (0.9)	3 (0.5)
Urinary tract infection	27 (0.9)	7 (0.7)	5 (0.8)
Upper respiratory tract infection	26 (0.9)	12 (1.2)	3 (0.5)
Cough	25 (0.8)	7 (0.7)	-
Osteoarthritis	19 (0.6)	-	-
Sinusitis	18 (0.6)	7 (0.7)	2 (0.3)
Back pain	18 (0.6)	7 (0.7)	2 (0.3)
Pharyngitis	17 (0.6)	6 (0.6)	3 (0.5)
Gastroenteritis	16 (0.5)	-	-
Hypertension	-	7 (0.7)	-
Vertigo	-	6 (0.6)	-
Eczema	-	-	2 (0.3)
Dermatitis allergic	-	-	2 (0.3)
Gastritis	-	-	1 (0.2)
Asthma	-	-	1 (0.2)
Dizziness	-	-	1 (0.2)
Abdominal pain upper	-	-	1 (0.2)
Herpes zoster	-	-	1 (0.2)
Headache	-	-	1 (0.2)
Benign prostatic hyperplasia	-	-	1 (0.2)
Blepharitis	-	-	1 (0.2)
Bronchitis chronic	-	-	1 (0.2)
Viral infection	-	-	1 (0.2)
Insomnia	-	-	1 (0.2)
Thermal burn	-	-	1 (0.2)
Urticaria	-	-	1 (0.2)
Injury	-	-	1 (0.2)
Abdominal pain lower	-	-	1 (0.2)
Myosclerosis	-	-	1 (0.2)
Myalgia	-	-	1 (0.2)
Dermatitis contact	-	-	1 (0.2)
Pain in extremity	-	-	1 (0.2)
Rhinitis	-	-	1 (0.2)
Seborrhoeic dermatitis	-	-	1 (0.2)
Cystitis	-	-	1 (0.2)
Gastric ulcer	-	-	1 (0.2)
Nasal congestion	-	-	1 (0.2)
Conjunctival haemorrhage	-	-	1 (0.2)
Basal cell carcinoma	-	-	1 (0.2)
Cervicobrachial syndrome	-	-	1 (0.2)
Myopia	-	-	1 (0.2)
Tooth impacted	-	-	1 (0.2)
Tinea pedis	-	-	1 (0.2)
Arteriosclerosis	-	-	1 (0.2)
Ear discomfort	-	-	1 (0.2)
Conjunctival hyperaemia	-	-	1 (0.2)
Reflux oesophagitis	-	-	1 (0.2)
Injection site haematoma	-	-	1 (0.2)
Skin infection	-	-	1 (0.2)
Muscle rupture	-	-	1 (0.2)
Cervix inflammation	-	-	1 (0.2)
Dysfunctional uterine bleeding	-	-	1 (0.2)
Reflux laryngitis	-	-	1 (0.2)
Angioedema	-	-	1 (0.2)
Hyperhidrosis	-	-	1 (0.2)

Counting rule applied: As there were more than 30 subjects per treatment group and ≤ 3 groups, only the 10 most frequent events in each treatment group are to be listed.
-: Implies that the event was not reported in the particular group or that the event was reported in the particular group but did not fall within the pre-defined counting rule of 10 most frequent events for that group.
Related = event assessed by the investigator as causally related to the study vaccination
* the 3 D-QIV groups and TIV-1 group were followed approximately 180 Days, the TIV-2 group was followed until Day 21

Safety Results: Number (%) of subjects with unsolicited adverse events within the 21-day (Days 0-20) post-vaccination period (Total Vaccinated cohort)

Most frequent adverse events - On-Therapy (occurring within Days 0-20 following vaccination)	**D-QIV Group N = 3036**	**TIV-1 Group N = 1010**	**TIV-2 Group N = 610**
Subjects with any AE(s), n (%)	379 (12.5)	138 (13.7)	92 (15.1)
Subjects with grade 3 AE(s), n (%)	39 (1.3)	7 (0.7)	2 (0.3)
Subjects with related AE(s), n (%)	64 (2.1)	26 (2.6)	14 (2.3)
Cough	48 (1.6)	14 (1.4)	9 (1.5)
Nasopharyngitis	43 (1.4)	17 (1.7)	9 (1.5)
Oropharyngeal pain	27 (0.9)	14 (1.4)	6 (1.0)
Rhinorrhoea	20 (0.7)	6 (0.6)	4 (0.7)
Headache	17 (0.6)	8 (0.8)	4 (0.7)
Upper respiratory tract infection	15 (0.5)	5 (0.5)	4 (0.7)
Bronchitis	14 (0.5)	-	3 (0.5)
Nasal congestion	12 (0.4)	4 (0.4)	-
Urinary tract infection	11 (0.4)	-	4 (0.7)
Back pain	11 (0.4)	-	-
Arthralgia	-	5 (0.5)	-
Dyspepsia	-	5 (0.5)	-
Sinusitis		4 (0.4)	-
Dizziness	-	-	4 (0.7)
Injection site haematoma	-	-	3 (0.5)
Rhinitis	-	-	3 (0.5)

Counting rule applied: As there were more than 30 subjects per treatment group and ≤ 3 groups, only the 10 most frequent events in each treatment group are to be listed.
-: Implies that adverse event was not reported in the particular group or that the adverse event was reported in the particular group but did not fall within the pre-defined counting rule of 10 most frequent events for that group.
Grade 3 = events which prevented normal every day activities.
Related = event assessed by the investigator as causally related to the study vaccination

Safety results: Number (%) of subjects with serious adverse events* during the entire study period (Total Vaccinated cohort)

Serious adverse event, n (%) [n considered by the investigator to be related to study medication]

All SAEs	**D-QIV Group N = 3036**	**TIV-1 Group N = 1010**	**TIV-2 Group N = 610**
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	70 (2.3) [0]	26 (2.6) [0]	1 (0.2) [0]
Cerebrovascular accident	5 (0.2) [0]	2 (0.2) [0]	0 (0.0) [0]
Myocardial infarction	5 (0.2) [0]	1 (0.1) [0]	0 (0.0) [0]
Pneumonia	3 (0.1) [0]	2 (0.2) [0]	0 (0.0) [0]
Cardiac failure congestive	3 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Gastric adenoma	3 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Arteriosclerosis	1 (0.0) [0]	0 (0.0) [0]	1 (0.2) [0]
Asthma	1 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Breast cancer	2 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Bronchiolitis	1 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Cardiac failure	2 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Cholelithiasis	2 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Gastric ulcer haemorrhage	2 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Gastroenteritis	1 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Inguinal hernia	1 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Intervertebral disc protrusion	2 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]

Nephrolithiasis	0 (0.0) [0]	2 (0.2) [0]	0 (0.0) [0]
Respiratory tract infection	2 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Urinary tract infection	2 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Vertigo	1 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Abdominal hernia	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Acute abdomen	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Acute myocardial infarction	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Acute respiratory failure	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Ammonia increased	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Anaemia	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Aortic aneurysm	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Arteriosclerosis coronary artery	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Arthralgia	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Atelectasis	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Atrial fibrillation	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Benign prostatic hyperplasia	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Bronchospasm	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Cardiac arrest	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Cardiac disorder	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Cardio-respiratory arrest	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Cardiopulmonary failure	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Carotid artery stenosis	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Central nervous system infection	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Colon cancer	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Coma hepatic	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Confusional state	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Coronary artery disease	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Death	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Dehydration	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Depressed level of consciousness	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Device related infection	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Diabetes mellitus	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Diplopia	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Dizziness	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Erysipelas	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Foot fracture	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Gastric cancer	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Gastric ulcer	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Groin abscess	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Head injury	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Headache	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Hepatic neoplasm malignant	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Hip fracture	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Intervertebral disc disorder	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Intestinal infarction	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Intracranial aneurysm	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Ischaemic stroke	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Jaundice	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Joint dislocation	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Ligament rupture	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Lumbar vertebral fracture	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Muscular weakness	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Myocardial ischaemia	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Non-cardiac chest pain	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Oesophagitis	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Osteomyelitis	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]

Pelvic fracture	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Pleurisy	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Pneumonia aspiration	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Pruritus	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Pulmonary hypertension	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Pyelonephritis acute	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Radius fracture	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Rectal cancer	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Renal cell carcinoma	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Respiratory failure	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Rotator cuff syndrome	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Small cell lung cancer stage unspecified	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Subarachnoid haemorrhage	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Sudden death	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Tendon rupture	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Thyroid cancer	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Tooth abscess	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Transient ischaemic attack	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Upper gastrointestinal haemorrhage	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Ureteric stenosis	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Urinary incontinence	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Vestibular disorder	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Fatal SAEs	**D-QIV Group N = 3036**	**TIV-1 Group N = 1010**	**TIV-2 Group N = 610**
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	9 (0.3) [0]	3 (0.3) [0]	0 (0.0) [0]
Myocardial infarction	2 (0.1) [0]	1 (0.1) [0]	0 (0.0) [0]
Cardiac arrest	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Cardiac disorder	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Cardiac failure congestive	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Cardio-respiratory arrest	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Cardiopulmonary failure	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Cerebrovascular accident	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Coma hepatic	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Death	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Intestinal infarction	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Pulmonary hypertension	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Small cell lung cancer stage unspecified	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Sudden death	1 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
* the 3 D-QIV groups and TIV-1 group were followed approximately 180 Days, the TIV-2 group was followed until Day 21			

Conclusion:

Lot-to-lot consistency for the three QIV lots:

The limits of the 2-sided 95% CI for the largest adjusted GMT ratios among the three lots of D-QIV were between 0.67 and 1.50 for the four strains.

Immunological non-inferiority of D-QIV versus TIV for the three strains included in each of the TIV vaccines:

The UL of the 2 sided 95% CI for the adjusted GMT ratio of TIV (pooled TIV-1 and TIV-2) over D-QIV was 1.18 for A/California/7/2009 and 1.07 for A/Victoria/210/2009. The UL of the 2 sided 95% CI for the adjusted GMT ratio of TIV-1 over D-QIV for the B/Brisbane/60/2008 strain was 1.07. The UL of the 2 sided 95% CI for the adjusted GMT ratio of TIV-2 over D-QIV for the B/Brisbane/3/2007 strain was 1.07.

The UL of the 2 sided 95% CI for the difference in SCR of TIV (pooled TIV-1 and TIV-2) minus D-QIV was 4.11% and -0.30% for A/California/7/2009 and A/Victoria/210/2009 respectively. The UL of the 2 sided 95% CI for the difference in SCR of TIV-1 minus D-QIV for the B/Brisbane/60/2008 strain was 1.83%. The UL of the 2-sided 95% CI for the difference in SCR of TIV-2 minus D-QIV for the B/Brisbane/3/2007 strain was 2.01%.

Immunological superiority of D-QIV versus TIV for the B strain that is not included in the TIV vaccines:

The LL of the 2-sided 95% CI for the adjusted GMT ratio of D-QIV over TIV-2 for the B/Brisbane/60/2008 strain was 1.42. The LL of the 2-sided 95% CI for the adjusted GMT ratio of D-QIV over TIV-1 for the B/Brisbane/3/2007 strain was 1.41.

The LL of the 2-sided 95% CI for the difference in SCR of D-QIV minus TIV-2 for the B/Brisbane/60/2008 strain was 5.70%.
The LL of the 2-sided 95% CI for the difference in SCR of D-QIV minus TIV-1 for the B/Brisbane/3/2007 strain was 11.54%.

At Day 0, the GMTs against the 4 influenza vaccine strains ranged from 14.7 to 101.4 in the D-QIV Group, from 15.6 to 100.9 in the TIV-1 Group and from 14.4 to 99.8 in the TIV-2 Group. At Day 21, the GMTs ranged from 201.1 to 601.8, from 218.4 to 393.8 and from 213.0 to 582.5 in the D-QIV, TIV-1 and TIV-2 groups, respectively. At the same time point, the percentage of subjects who seroconverted for HI antibodies against the 4 influenza vaccine strains ranged from 58.1% to 77.5% in the D-QIV Group, from 45.6% to 77.2% in the TIV-1 Group and from 47.5% to 80.2% in the TIV-2 Group.
During the 21-day post-vaccination period, 379 (12.5%), 138 (13.7%) and 92 (15.1%) subjects in the D-QIV, TIV-1 and TIV-2 groups, respectively, reported at least one unsolicited AE.
During the entire study period (up to Day 180 for the D-QIV and the TIV-1 group and up to Day 21 for the TIV-2 group), 70 (2.3%), 26 (2.6%) and 1 (0.2%) subjects in the D-QIV, TIV-1 and TIV-2 groups, respectively, reported at least one SAE; fatal SAEs were reported for 9 (0.3%) and 3 (0.3%) subjects of the D-QIV and TIV-1 groups, respectively. All the SAEs (fatal and non-fatal) were assessed by the investigator as not causally related to the study vaccination.

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