DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

STATISTICAL REVIEW AND EVALUATION
BLA

BLA/Supplement Number:	125127/513
Product Name:	Fluarix® Quadrivalent, Influenza Virus Vaccine
Indication(s):	Active immunization for the prevention of disease caused by the 2 influenza A virus subtypes and the 2 influenza B virus types contained in the vaccine for use in persons 3 years of age and older
Applicant:	GlaxoSmithKline (GSK) Biologicals, Rixensart, Belgium
Submission Date(s):	05/24/2012
Review Priority:	Standard
Statistical Branch:	OBE/DB/VEB
Primary Statistical Reviewer:	Ghideon Ghebregiorgis, Ph.D. _____ Date
Concurring Reviewer (1):	Tsai-Lien Lin, Ph.D. _____ Date
Concurring Reviewer (2):	A. Dale Horne, Dr.P.H. _____ Date
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1. EXECUTIVE SUMMARY

GSK has developed a seasonal quadrivalent inactivated influenza vaccine formulation, which includes the two recommended A strains, the recommended B strain, and a second B strain of the complementary B lineage. This vaccine is inactivated split-virion quadrivalent influenza vaccine formulation (referred to as D-QIV throughout this memo) containing the influenza antigens as included in the Fluarix BLA (STN 125127), produced in Dresden (Germany). The candidate D-QIV vaccine includes the H1N1 and H3N2 A strains and two B strains, one of the Yamagata lineage and one of the Victoria lineage. The candidate vaccine contains 15µg HA per strain, for a total of 60µg HA per 0.5 ml dose.

The current BLA supplemental (sBLA) is submitted to request approval of GSK's quadrivalent influenza virus vaccine (D-QIV) as an additional formulation under the FLUARIX license (STN 125127). The data provided in this sBLA include clinical, labeling, non-clinical, CMC and establishment information to support licensure of the candidate D-QIV vaccine. The request of approval is based on two supportive phase I/II studies and the following two pivotal phase III studies:

- **Study D-QIV-008** (N=3036 received D-QIV): is a lot-to-lot consistency, immunogenicity (non-inferiority to TIV and superiority of 4th strain) and safety study in persons 18 years and older, titled:

  "*A phase III randomized, partially-blind, controlled, multi-country, multi-centre study to evaluate the immunogenicity, reactogenicity and safety of GSK Biologicals' quadrivalent influenza vaccine D-QIV (GSK2321138A) and to evaluate the clinical consistency of three production lots of D-QIV in terms of immunogenicity, when administered intramuscularly to adults 18 years of age and older*".

- **Study D-QIV-003** (N= 1192 received D-QIV): is an immunogenicity (non-inferiority to TIV and superiority of 4th strain) and safety study in children 3 to 17 years of age with an observational arm in children 6-35 months of age, and is titled:

  "A phase III, double-blind, randomized study to evaluate the immunogenicity and safety of GSK Biologicals' quadrivalent influenza vaccine compared to GSK Biologicals' trivalent influenza vaccine administered intramuscularly in children aged 3 to 17 years and to describe the safety and immunogenicity of GSK Biologicals' quadrivalent influenza vaccine in children aged 6 to 35 months".

Refer to table 1 in section 1.2 of this memo for a summary of the main features of the four studies submitted to support the application.

This review memo contains a statistical review, statistical comments and recommendations of the sBLA submission.

Statistical bioassay review and comments are not included in this memo. A separate review memo for bioassay is available on EDR.

1.1 Conclusions and Recommendations

Based on the statistical analyses and criteria described in chapter 1 (section 1.3) and chapter 3 of this review, the data support the following overall conclusions.

The pre-specified criteria for:

- Lot-to-lot consistency in terms of Geometric Mean Titer (GMT) ratio were met for the three considered lots of D-QIV for the primary objective of D-QIV lot to lot consistency.
- Immunological non-inferiority of D-QIV for each of the four strains relative to TIV vaccines with respect to GMT ratio and Seroconversion Rate (SCR) difference were met for subjects 3 years and older.
- Immunological superiority of D-QIV over the TIV for the B strain that is not included in the TIV vaccines with respect to GMT ratio and SCR difference were met for subjects 3 years and older.

The safety profile of the D-QIV vaccine has been established based on results obtained in a total of 4,631 D-QIV vaccine recipients including 1,490 children and 3,141 adults. Of these, 1,192 children (915 children 3-17 years of age, and 277 children 6-35 months of age) and 3,036 adults (including 1,505 elderly subjects >64 years of age) participated in the two Phase III studies submitted within this BLA.

Safety results have shown that the reactogenicity and safety profile of the D-QIV vaccine is similar to the profile of the licensed trivalent Fluarix vaccine and is also similar to the trivalent influenza vaccine (TIV-2) containing the B strain from the alternate lineage, in subjects above 3 years of age.

No safety concerns were raised based on the 6-months follow-up and no reported SAE was considered as vaccine-related.

Recommendation:
The data support the conclusion that, in subjects 3 years of age and older, the D-QIV candidate vaccine appears to provide non-inferior immunogenicity, compared to the licensed trivalent Fluarix vaccine, against four influenza strains.

Based on safety analysis findings it can be concluded that increasing the total antigen content by adding a fourth strain in the D-QIV vaccine does not appear to have a negative impact on the reactogenicity and safety profile relative to the trivalent Fluarix vaccine.

1.2 Brief Overview of Clinical Studies and contents of the BLA

The submission contains results of 4 clinical studies, two phase 1/2 (D-QIV-001 and D-QIV-002) supportive studies and two pivotal phase III studies (D-QIV-008 and D-QIV-003). The main features of each study are summarized in table 1.

Two pivotal, Phase III, studies, study D-QIV-008 and study D-QIV-003, evaluated the candidate D-QIV vaccine in adults and children from 3 years of age. Both studies included two comparator

groups, one receiving the trivalent influenza vaccine containing the strains recommended for the ongoing season, and one a second trivalent vaccine that contained a strain of the B lineage not included in the seasonal vaccine.

Study D-QIV-003 enrolled an additional group of 6 to 35-month old children for exploratory purposes. This group received open-label D-QIV vaccine.

Two supportive studies, study D-QIV-001 (Phase I/II) and study D-QIV-002 (Phase II), evaluated the candidate vaccine in adults and children from 18 months of age. These studies included a control group that received the seasonally recommended trivalent influenza vaccine

Table1: Summary of Clinical studies submitted to support the BLA

Type of Study	Study Identifier	Country (year)	Population	Objective(s) of the Study	Study Design	Test Product(s); Dosage Regimen; Route of	Number of Subjects
Phase III	D-QIV-008	US, Germany, Romania, Spain, Korea, Taïwan (2010-2011)	Adults ≥18 years	Immunogenicity (lot-to-lot consistency of D-QIV (GMT), non-inferiority to TIV vaccine (GMT/SCR); superiority to 4th strain (GMT/SCR), Reactogenicity and Safety	Randomized, partially blind, controlled 5 parallel groups	D-QIV[a] groups: - D-QIV-1 (lot 1), - D-QIV-2 (lot 2), - D-QIV-3 (lot 3) Control groups: - *Fluarix* - TIV-2[b] 1 dose administered IM on Day 0	D-QIV groups: 3036 (~1000/lot) *Fluarix*: 1010 TIV-2: 610
Phase III	D-QIV-003	US, Germany, Czech Republic, France, Philippines (2010-2011)	Children 6 months - 17 years	Immunogenicity: non-inferiority to TIV vaccine (GMT/SCR) (3-17 years), superiority of 4th B strain (GMT/SCR) (3-17 years) Reactogenicity and safety	Randomized, double-blind, 3 parallel groups	D-QIV[a] (6m - 17Y) - *Fluarix* (3-17Y) - TIV-2[b] Primed children: 1 IM dose at D0 Unprimed children: 2 IM doses at D0 and D28	D-QIV 3-17Y : 915; D-QIV 6-35m : 277 *Fluarix* : 912 TIV-2 : 911
Phase II	D-QIV-002	Mexico (2009-2010)	Children 18-47 months	Immunogenicity, non-inferiority to TIV vaccine (GMT), superiority of 4th B strain (GMT) Reactogenicity and safety	Randomized, double-blind, multi center, 4 parallel groups Primed subjects previously vaccinated with	- D-QIV[a] (primed) - D-QIV(unprimed) - Fluarix (primed) - Fluarix (unprimed) Primed subjects: one dose at D0 Unprimed subjects: 2 doses at D0 and D28;	95 203 97 204
Phase I/II	D-QIV-001	Czech Republic (2008- 2009)	Adults 18-60 years	-Immunogenicity: non-inferiority to TIV vaccine, (GMT), superiority of 4th B strain (GMT) - Reactogenicity and safety	Randomized, single-blind, single center, controlled 4 parallel groups	- D-QIV, *Fluarix* - ----------(b)(4)---------- - ---------- ---(b)(4)--------- 1 dose administered IM on Day 0	105 subjects per group

[a] D-QIV: GSK's quadrivalent influenza candidate vaccine

[b] TIV-2 refers to a trivalent, Fluarix formulation containing the alternative lineage B strain (as contained in D-QIV) instead of the WHO/CBER recommended strain.

[c] ----------(b)(4)----------

1.3 Major Statistical Issues and Findings

The basis for sample size calculation was specified in the protocols of the four D-QIV studies presented. In pivotal studies (D-QIV-003, D-QIV-008), target sample sizes were calculated per-protocol such that the overall power to conclude on primary objectives of the respective studies was 90% or greater.

The study protocols pre-defined consistency, non-inferiority and superiority criteria as follows:

- For concluding on consistency among D-QIV vaccine lots in pivotal study DQIV-008, the pre-defined criterion was that the 95% confidence intervals (CI) for the pair-wise adjusted geometric mean ratios (adjusted for the baseline titer) of HI antibody titers were to be contained within the [0.67; 1.5] interval.
- In pivotal studies D-QIV-003 and -008, conclusion on the non-inferiority of the D-QIV vaccine to *Fluarix* and to the TIV-2 vaccine was based on HI antibody GMTs and seroconversion rates (SCR) according to the following pre-defined criteria:
  - The upper limit of the two-sided 95% CI for the ratio of GMTs (*Fluarix* or TIV-2 vaccine over the D-QIV vaccine) was not to exceed 1.5 for each strain included in *Fluarix* and in the TIV-2 vaccine, and
  - The upper limit of the two-sided asymptotic standardized 95% CI for the difference in SCR (*Fluarix* or TIV-2 vaccine minus D-QIV vaccine) was not to exceed 10% for each strain included in *Fluarix* and the TIV-2 vaccine.
- In supportive D-QIV studies, the criterion to conclude on non-inferiority was:
  - The lower limit of the two-sided 95% CI for the GMT ratio (D-QIV vaccine over TIV vaccine) was to be not less than 0.67 (D-QIV-001)
  - The upper limit of the two-sided 95% CI for the GMT ratio (*Fluarix* over D-QIV vaccine) was not to exceed 2 (D-QIV-002)
- In pivotal studies D-QIV-003 and -008, conclusion on superiority for the additional B strain was based on HI antibody GMTs and seroconversion rates according to the following the pre-defined criteria:
  - The lower limit of the two-sided 95% CI on the GMT ratio (D-QIV vaccine over *Fluarix* or TIV-2 vaccine) was to be greater than 1, and
  - The lower limit of the two-sided 95%CI for the difference in SCR (D-QIV vaccine minus *Fluarix* or TIV-2 vaccine) was to be greater than 0
- In supportive studies D-QIV-001 and D-QIV-002, the criterion to conclude superiority for the additional B strain was the lower limit of the two-sided 95% CI for the ratio of GMT (D-QIV vaccine over TIV vaccine) to be above 1.

All the pre-specified criteria were met for both primary and secondary endpoints specified in the two pivotal studies included in this BLA (Study D-QIV-008 and D-QIV-003).

In each of the pivotal studies, descriptive analyses of immunogenicity calculated HI antibody GMTs, seropositivity rates, seroprotection rates; seroconversion rates and seroconversion factors with 95% confidence intervals, for each influenza strain and each group were included.

An analysis of the immune response stratified by age was performed in the two pivotal studies:

- In the 18-64 years and ≥65 years age groups, 18-60 and >61 years age groups, and 18-74 and ≥75 years in study D-QIV-008
- In the 3-8 years and 9-17 years age groups; and in the 6-17 months and 18-35 months age groups in study D-QIV-003

In study D-QIV-003, analyses of the HI immune response were performed:

- According to priming status (defined by previous influenza vaccination/infection status) and age (3-8 years; 9-17 years)
- According to baseline sero-status and age (3-8 years; 9-17 years and 9-12 years; 13-17 years)

Immunogenicity and safety sub group analysis by age, gender, race and region for both studies are included in sections 3.1 and 3.2.

2. INTRODUCTION

2.1 Overview

2.1.1 History of Product Development

GSK Biologicals has been marketing an inactivated trivalent influenza split vaccine (*Fluarix*) since 1992 in Europe and since 2005 in the United States. The vaccine is registered in more than 100 countries and more than 300 million doses have been distributed.

GSK has now developed a candidate inactivated, split virion quadrivalent influenza vaccine formulation (D-QIV), containing 15µg Haemagglutinin (HA) of each of four antigenically-distinct influenza virus strains per 0.5 mL dose (i.e. 60 µg total HA per dose), including the three influenza strains (A/H1N1, A/H3N2 and B) recommended annually by CBER)/ World Health Organization (WHO), and a second B strain of the complementary B lineage. The three recommended strains are the same as those included in *Fluarix* (STN 125127), and the additional B strain is produced in the same facilities (i.e., Dresden, Germany), according to the same manufacturing process.

2.1.2 Class and Indication

The vaccine is indicated for active immunization of adults and children from 3 years of age against influenza disease caused by the two influenza A virus subtypes and the two influenza B virus types contained in the vaccine.

The applicant proposed the vaccine to be administered as a single 0.5 ml injection. Children 3 to less than 9 years of age who have not previously been vaccinated against influenza should receive a second dose of 0.5 ml after an interval of at least 4 weeks.

2.2 Data Sources

Data sources including all materials reviewed (applicant's study reports, data sets analyzed, and literature referenced) are provided electronically and are available in the EDR on the following link:

----------(b)(4)----------

3. STATISTICAL EVALUATION

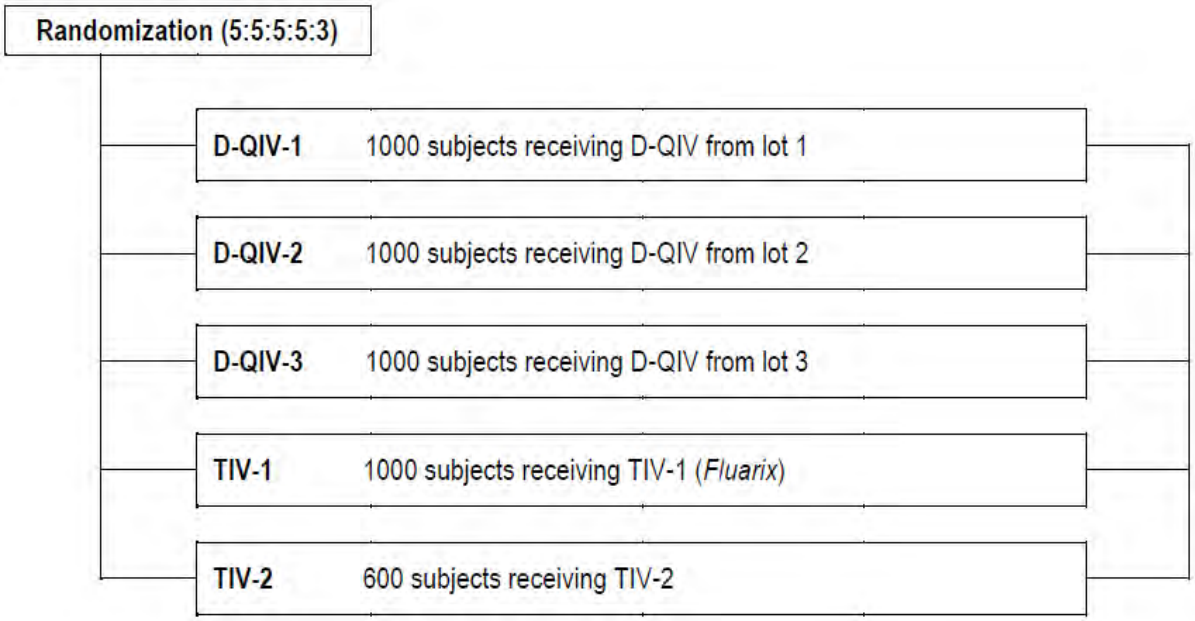
3.1 Study D-QIV-008

3.1.1 Study Design

The study was a randomized, partially-blinded, controlled, multi-center, multi-country study with five study arms: D-QIV-1, D-QIV-2, D-QIV-3 (three production lots of D-QIV), TIV-1 (*Fluarix*, a licensed TIV containing the strains recommended by CBER/ WHO for the Northern Hemisphere 2010-2011 season), and TIV-2 which represented a formulation containing the alternate B lineage strain not represented in the Northern Hemisphere 2010-2011 season recommendation, but otherwise identical to *Fluarix*.

Subjects were randomized (5:5:5:5:3), with D-QIV being assessed in 3000 subjects (1000 subjects per lot) and 1600 subjects receiving either one of the two formulations of TIV. Immune response was evaluated on Day 21 relative to Day 0 in a sub-cohort of subjects. All subjects were followed for reactogenicity and safety for up to 6 months after vaccination, except the subjects from the TIV-2 group, who were followed for 21 days. After Visit 2, their participation in the study was complete so they still had the opportunity to be vaccinated with the seasonal vaccine containing the recommended B strain before the influenza season.

Fig. 1: Overview of the study design



Day 0 Visit 1	Day 21 Visit 2	Day 180 Phone Contact 3
– Blood Sample – Vaccination	– Blood sample – Safety Follow up – Study conclusion – Study end for subjects of the TIV-2 group	– Safety follow up – Study conclusion

3.1.1.1 Objectives and Hypothesis

Co-Primary Objectives:

- To assess the lot-to-lot consistency of three lots of D-QIV vaccine in terms of hemagglutination inhibition (HI) antibody geometric mean titers (GMTs).

  Criterion to evaluate lot-to-lot consistency:- Lot-to-lot consistency is demonstrated if, for each vaccine strain, the limits of the two-sided 95% Confidence Interval (CI) for the largest geometric mean ratio (GMR) among the three lots was 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 (*Fluarix*) and TIV-2 vaccines for the three strains that were included in each of TIV-1 (*Fluarix*) and TIV-2 vaccines.

  Criteria to conclude non-inferiority: Non-inferiority in terms of GMTs and SCR is demonstrated if the upper limit of the two-sided 95% CI for the ratio of GMT of TIV-1 (Fluarix) vaccine or TIV-2 vaccine over D-QIV vaccine did not exceed 1.5 for each strain that was included in the TIV-1 (Fluarix) and TIV-2 vaccines.

  And

  if the upper limit of the two-sided asymptotic standardized 95% CI for the ifference in SCR (TIV-1 [Fluarix] vaccine or TIV-2 vaccine minus D-QIV vaccine) did not exceed 10% for each strain that was included in the TIV-1 (Fluarix) 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 (*Fluarix*) 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 two-sided 95% CI on GMT ratio (D-QIV vaccine over TIV-1 [Fluarix] vaccine or D-QIV vaccine over TIV-2 vaccine) was greater than 1 and the lower limit of the two-sided 95% CI for the difference in SCR (D-QIV vaccine minus TIV-1 [Fluarix] vaccine or TIV-2 vaccine) was greater than 0.

Secondary objectives

- To describe the immunogenicity of D-QIV vaccine, TIV-1 (*Fluarix*) vaccine and TIV-2 vaccine in terms of GMTs and seroprotection rate (SPR) at Days 0 and 21, and SCR and mean geometric increase (MGI) at Day 21 overall and in each age stratum.
- To assess the reactogenicity and safety of D-QIV, TIV-1 (*Fluarix*) and TIV-2 vaccines overall and in each age stratum in terms of:
  - Solicited local symptoms during the 7-day post-vaccination follow-up (day of vaccination and 6 subsequent days).
  - Solicited general symptoms during the 7-day post-vaccination follow-up (day of vaccination and 6 subsequent days).
  - Unsolicited symptoms during the 21-day (day of vaccination and 20 subsequent days) post-vaccination follow-up period.
  - Serious adverse events (SAEs), adverse events (AEs) with medically attended visit (MAV) and potential immune mediated diseases (pIMDs) during the entire study period.

Endpoints

The endpoints associated with the co-primary and secondary objectives are as follows.

Primary endpoints:
Humoral immune response in terms of HI antibodies

- Serum HI antibody titers against the four 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 titer <1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥ 1:10 and at least a four-fold increase in post-vaccination titer.

Secondary endpoints

Immunogenicity endpoints

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

SPR is defined as the percentage of vaccinees with a serum HI titer ≥ 1:40 that usually is accepted as indicating protection.
MGI is defined as the geometric mean of the within subject ratios of the post-vaccination reciprocal HI titer to the Day 0 reciprocal HI titer.

Safety/Reactogenicity endpoints

- Solicited local 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.
- SAEs, AEs with MAV and pIMD: Occurrence and relationship to vaccination during the entire study period in each group.

3.1.1.2 Population selection and Determination of Sample Size

3.1.1.2.1 Selection of Study Population

The study was a multi-center study conducted in Germany, Romania, Spain, Korea, Taiwan and the United States.

The target number of subjects was 4600 overall: 1000 subjects in each D-QIV group, 1000 subjects in the TIV-1 group and 600 subjects in the TIV-2 group. Only a sub-cohort of subjects was included in the immunogenicity analysis. The immunogenicity sub-cohort was to include the first 600 subjects enrolled in each treatment group taking into account the age stratification and the minimization factors, therefore 3000 subjects in total (600 subjects receiving each lot of D-QIV, 600 subjects receiving TIV-1 [Fluarix] and 600 subjects receiving TIV-2).

The overall sample size for the study was determined by the safety cohort needed to achieve a sample size of 3000 subjects receiving the candidate vaccine to allow detection of rare events occurring at a rate of 0.01%.

Inclusion criteria

All subjects had to satisfy ALL the following criteria at study entry:

- A male or female 18 years of age or older at the time of vaccination.
- Subjects who the investigator believed that they/their parent(s)/ LAR(s) could and would comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
- Written informed consent obtained from the subject/from the parent(s) or legally acceptable representative (LAR) before any study procedure. Written informed assent obtained from the subject if/as required by local regulations.
- Healthy subjects or those with chronic well-controlled disease as established by physical examination before entering into the study.
- Female subjects of non-childbearing potential could be enrolled in the study. Non-childbearing potential was defined as current tubal ligation, hysterectomy, ovariectomy or post-menopause[1].
- Female subjects of childbearing potential could be enrolled in the study, if the subject:
    - had practiced adequate contraception for 30 days prior to vaccination, and
    - had a negative pregnancy test on the day of vaccination, and
    - had agreed to continue adequate contraception during the entire treatment period and for 2 months after completion of the vaccination series.

Exclusion criteria

The following criteria had to be checked at the time of study entry. If any exclusion criterion applied, the subject was not to be included in the study:

- Child in care.

1 Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years.

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccines within 30 days preceding the dose of study vaccine, or planned use during the study period.
- Chronic administration (defined as more than 14 days in total) of immuno-suppressants or other immune-modifying drugs within six months prior to the first vaccine dose. For corticosteroids, this meant prednisone ≥ 20 mg/day, or equivalent. Inhaled and topical steroids were allowed.
- Administration of an influenza vaccine during the 6 months preceding entry into the study.
- Planned administration/administration of a vaccine not foreseen by the study protocol within 30 days before vaccination and up to Visit 2.
- Any contra-indication to intramuscular (IM) administration of the influenza vaccines.
- History of hypersensitivity/anaphylaxis to a previous dose of influenza vaccine, history of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccines including latex.
- Any administration of a long-acting immune-modifying drug (e.g. rituximab, infliximab) within 3 months before study start, or planned administration during the study period.
- Any confirmed or suspected immunosuppressive or immuno-deficient condition, based on medical history and physical examination (no laboratory testing was required).
- Acute disease and/or fever at the time of enrolment.
    - Fever was defined as temperature ≥ 37.5°C (99.5°F) on oral or axillary setting. The preferred route for recording temperature in this study was axillary.
    - Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever could be enrolled at the discretion of the investigator.
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.
- History of Guillain–Barré syndrome (GBS).
- Administration of immuno-globulins and/or any blood products within the 3 months preceding the first dose of study vaccine or planned administration during the study period.
- Pregnant or lactating female.
- History of chronic alcohol consumption and/or drug abuse.
- Any condition which, in the opinion of the investigator, prevented the subject from participating in the study.

3.1.1.2.2 Sample size Determination

The sample size in the immunogenicity sub-cohort was 570 evaluable subjects for each group in order to reach the global power of at least 90% for all co-primary objectives.

The overall sample size for the study was determined by the need to achieve an overall sample size of 3000 subjects receiving the candidate vaccine to allow detection of rare events occurring at a rate of 0.01%. Therefore 3000 subjects were to be enrolled in the D-QIV group (1000 per lot) and 1000 in the TIV-1 group.

Tables 3-7 shows the minimum power to detect equivalence in HI antibody GMTs between lots, power to detect a non-inferiority in HI antibody GMTs between D-QIV and TIV-1 or TIV-2 groups, power to detect a non-inferiority in SCR difference between D-QIV and TIV-1 or TIV-2 vaccines, power to detect superiority in HI antibody GMTs between D-QIV and TIV-1 (*Fluarix*) or TIV-2 vaccines for the second B strain present in D-QIV, power to detect superiority in SCR difference between D-QIV and TIV-1 or TIV-2 vaccines for the second B strain present in D-QIV vaccine respectively.

Table 3: Minimum power to detect equivalence in HI antibody GMTs between lots

Number of evaluable subjects in each lot	StdDev[1]	Assumed 95% CI on the GMT ratio	One comparison		Number of comparisons for all strains	Overall	
			Beta	Power[2]		Beta	Power[3]
570	0.6	]0.67-1.5[	0.00138	99.9%	4	0.00552	99.4%

[1] Standard deviation of the log of titers observed in study Flu D-QIV-001.
[2] Power estimated using equivalence test of two means using differences, alpha = 5%
[3]Using Bonferroni adjustment on type II error (overall beta=sum of type II error of each endpoint)

Table 4: Power to detect non-inferiority in HI antibody GMTs between D-QIV and TIV-1 or TIV-2.

Strains	Number of evaluable subjects in D-QIV group	Number of evaluable subjects in TIV-1 and/or TIV-2 group	Assumed UL of 95% CI on the GMT ratio	StdDev[1]	Power to success (1 test)[2]	Power to success (2 tests)[3]
A strains	1710	1140	1.5	0.6	>99.99%	>99.99%
B strains	1710	570	1.5	0.6	>99.99% (beta=0.00002	>99.99% (beta=0.00004

[1]Standard deviations of the log of titers observed in study Flu D-QIV-001.
[2]Power estimated using equivalence test of 2 means using differences, alpha = 5%
[3]Using Bonferroni adjustment on type 2 error (overall beta=sum of type II error of each endpoint)

Table 5: Power to detect non-inferiority in SCR difference between D-QIV and TIV-1 or TIV-2

Strains	Number of evaluable subjects in D-QIV group	Number of evaluable subjects in TIV-1 and/or TIV-2 group	Proportion in each TIV group[1]	Proportion in the D-QIV group[2]	Assumed UL of 95% CI on the difference in SCR	Power to success (1 test)[3]	Power to success (2 tests)[4]
A strains	1710	1140	0.5	0.5	10%	99.95% (beta=0.0005)	99.9% (beta=0.001)
B strains	1710	570	0.5	0.5	10%	98.5% (beta=0.0148)	97.0% (beta=0.0296)

[1,2]SRC observed in study Flu D-QIV-001 for subjects 18-60 years old.
[3]Power estimated using one-sided T-test on the difference of proportions, alpha = 2.5%
[4]Using Bonferroni adjustment on type 2 error

Table 6: Power to detect superiority in HI antibody GMTs between D-QIV and TIV-1 or TIV-2 vaccines for the second B strain present in D-QIV

Number of evaluable subjects in D-QIV group	Number of evaluable subjects in TIV-1 or TIV-2 groups	Assumed difference between GMTs	Power to success (1 test)[1]	Power to success (2 tests)[2]
1710	570	1.5 fold	>99.9% (beta=0.00002)	>99.9% (beta=0.00004)

[1] Power estimated using one-sided two-sample t-test for difference of means, alpha 2.5%.
[2] Using Bonferroni adjustment on type 2 error.

Table 7: Power to detect superiority in SCR difference between D-QIV and TIV-1 or TIV-2 vaccines for the second B strain present in D-QIV vaccine

Number of evaluable subjects in D-QIV group	Number of evaluable subjects in TIV-1 or TIV-2 groups	Proportion in the TIV-1 or TIV-2 group	Power to success (1 test)[1]	Power to success (2 tests)[2]
1710	570	0.5	98.6% (beta=0.0136)	97.3% (beta=0.0272)

[1] Power estimated using one-sided two-sample t-test for difference of means, alpha 2.5%.
[2] Using Bonferroni adjustment on type 2 error.

3.1.1.3 Statistical Analysis Planned in the Protocol

3.1.1.3.1 Statistical Analysis

Analysis of Demographics

As stated in the protocol demographic characteristics (age, gender and race) of each study cohort were tabulated by treatment group and overall.

The mean ages (in months, with range and standard deviation) by gender of the enrolled subjects, as a whole, and per group, were calculated. History of any influenza vaccination within the previous 3 seasons was also tabulated.
The distribution of subjects enrolled among the study sites was tabulated as a whole and per group. All demography analysis was also performed according to age strata.

Analysis of immunogenicity

The primary analysis was based on the according to the protocol (ATP) cohort for analysis of immunogenicity. Per the protocol if the percentage of subjects excluded from this ATP cohort for analysis of immunogenicity was greater than 5%, a second analysis based on the total vaccinated cohort (TVC) had to be performed to complement the ATP analysis.

Per the protocol the following within group and between group assessments are conducted.

A. Within group assessment

For the humoral response in terms of HI antibodies for all vaccine strains, the following parameters were calculated by group for all subjects and for each age stratum:

- GMTs of HI at Days 0 and 21 with 95% CI.
- SCR at 21 days following the vaccination with exact 95% CI.

- SPR at Days 0 and 21 with exact 95% CI.
- MGI at 21 days following the vaccination with 95% CI.

B. Between group assessments

The following analyses were performed for each vaccine strain:

- The adjusted GMTs were estimated using an Analysis of Covariance (ANCOVA) model fitted on log10 transformed post-vaccination HI titer including treatment as fixed effect and baseline as covariate. The treatment groups included D-QIV-1, D-QIV-2, D-QIV-3, TIV-1 and TIV-2.
- GMT ratios (with two-sided 95% CI) related to the comparisons of interest (see objectives, QIV as denominator for non-inferiority; TIV-1 [*Fluarix*] or TIV-2 as denominator for superiority) were computed.
- The SCR of each vaccine, the SCR difference and the two sided 95% CI of the SCR differences were computed after fitting a logistic regression on the seroconversion response, including the vaccine group as fixed effect and the pre-vaccination concentration as covariate.
- The assumption that the treatment effect did not depend on the pre-vaccination serological level was checked by ANCOVA and logistic regression models and additional analyses were to be performed in case of evidence of interaction.

Analysis of safety

According to the protocol the primary analysis was performed on the TVC. If the percentage of subjects excluded from the ATP cohort for analysis of safety was greater than 5%, a second analysis had to be performed on this ATP cohort to complement the analysis of the TVC.

The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the solicited follow-up period was tabulated with exact 95% CI.
The same tabulation was done for grade 3 AEs, related AEs and grade 3 related AEs.

3.1.1.3.2 Protocol Amendments/Modifications

The original protocol dated June 18, 2010 was amended twice, once on July 23rd, 2010 and then on October 19th, 2010. The applicant provided the following rationale for these amendments:

Amendment 1 (23 July 2010):
This amendment was developed for Korea and Taiwan, where the legal age of majority is 20 years. Local regulations required the informed consent be signed by the subject's parent(s)/ LAR(s) for study participants younger than 20 years.

Amendment 2 (19 October 2010):
Guillain-Barré syndrome (GBS) is a rare autoimmune disorder, the incidence of which was estimated to be 0.6–4/100,000 person/year worldwide. Often, GBS occurs a few days or weeks after the patient has had symptoms of a respiratory or gastrointestinal microbial infection.

GBS has been a focus of influenza vaccine safety monitoring since 1976, when an increased risk was found with the swine origin influenza vaccine [Schonberger, 1979]. Controlled studies since 1976 have demonstrated either no or a slight elevated risk of GBS following seasonal influenza vaccination (approximately 1 additional case/million vaccinations) [Vellozzi, 2010]. Using the vaccine adverse event reporting system (VAERS), a US spontaneous reporting system, a recent analysis demonstrated no difference in any age group in proportional reporting of GBS following 2009-H1N1vaccination compared with the 2009–2010 seasonal influenza vaccine [Vellozzi, 2010].

Preliminary results from an analysis in EIP (CDC's Emerging Infections Program) comparing GBS patients hospitalized through March 31, 2010, who did and did not receive 2009 H1N1 vaccination showed an estimated age-adjusted rate ratio of 1.77 (GBS incidence of 1.92 per 100,000 person-years among vaccinated persons and 1.21 per 100,000 person-years among unvaccinated persons). If end-of-surveillance analysis confirmed this finding, this would correspond to 0.8 excess cases of GBS per 1 million vaccinations, similar to that found in seasonal influenza vaccines [Surveillance for Guillain-Barré Syndrome, 2010]. The 2009 H1N1 vaccine safety profile was similar to that for seasonal influenza vaccines, which had an excellent safety record.

Interim analysis of an ongoing observational study in Germany showed a potential link between vaccination with the pandemic A/California H1N1 vaccine and risk of GBS (or relapse of GBS). Further analyses were however needed to better understand this finding. In the meantime, as a precautionary measure, the Paul Erhlich Institute (PEI) recommended GSK to not enroll (exclude) subjects with any history of GBS into (from) this current study.

Subjects already enrolled in this study with history of GBS were to be followed for safety and immunogenicity as per protocol amendment 1 dated 23 July 2010.

Additionally, administrative changes including the addition of the Investigational New Drug (IND) number, addition of contributing authors, and change of sponsor contact name and correction of typing errors were made.

Other changes

Based on statistical reviewer's request during the October 21, 2010 meeting of this IND, an analysis of safety based on the TVC and an analysis of immunogenicity based on the ATP cohort for immunogenicity by gender and race (with a minimum of 10% of the total number of subjects per race category) were planned.

Comments:

1. *The protocol stated that temperatures ≥ 39.0°C /102.2°F were scored as grade 3 fever; however, in the statistical analysis, temperatures > 39.0°C /102.2°F were scored as grade 3 fever.*
2. *The protocol stated that the TVC for analysis of safety would include all subjects with at least one documented vaccine administration. Since there was only one dose administered, the analysis included all subjects with documented vaccine administration.*

3.1.2 Study Population Results

3.1.2.1 Number of Subjects

In total, 4656 subjects were vaccinated in this study: 3036 subjects in the D-QIV group, 1010 in the TIV-1 group and 610 in the TIV-2 group. From the 3036 subjects vaccinated in the D-QIV group, 1012 were vaccinated in the D-QIV-1 group, 1013 in the D-QIV-2group and 1011 in the D-QIV-3 group.

The number of subjects by center and the distribution of subjects by center and by vaccine lots received are provided in the study report. (Please refer to supplement 1 and Supplement 2 tables on pages 189 and 191 of the applicant's study report)

3.1.2.2 Study Completion and Withdrawal from Study

Overall, 4597 subjects completed the study and 57 subjects were withdrawn.
Table 8 provides the number of subjects vaccinated, completed and those withdrawn by study group.

Table 8: Number of subjects vaccinated, completed and withdrawn (TVC)

	D-QIV	TIV-1	TIV-2	Total
Number of subjects vaccinated	3036	1010	610	4656
Number of subjects completed	2994	997	606	4597
Number of subjects withdrawn	40	13	4	57
Number of subjects with unknown completion status	2	0	0	2

A total of 13 subjects withdrew from the study because of SAEs and one because of non-serious AE (refer to section 3.1.3 (Safety analysis results) for more details). No subject was lost due to protocol violation, move from study area and failure of inclusion criteria.

Table 9 shows the number of subjects withdrawn from the study and reason of withdrawal by study group

Table 9: Number of subjects withdrawn by reason of withdrawal and group (TVC)

Reason of withdrawal	D-QIV	TIV-1	TIV-2	Total
Serious Adverse Event	10	3	0	13
Non-Serious Adverse Event	0	0	1	1
Consent withdrawal (not due to AE)	9	5	3	17
Lost to follow up (subjects with complete vaccination course)	19	3	0	22
Other- Exclusion criteria	0	1	0	1
Other- No contact in protocol time[1]	0	1	1	1
Other- Not reachable by phone	1	0	0	1
Other- Not responding to telephone	1	0	0	1

[1]No contact during the scheduled (per protocol) day 180 contact time

3.1.2.3 Protocol Deviations

18 subjects (13 in the D-QIV group, 2 in the TIV-1 group and 3 in the TIV-2 group) were eliminated from the ATP cohort for safety due to administration of vaccine(s) forbidden in the protocol, randomization failure or study vaccine dose not administered according to protocol.

82 subjects (52 in the D-QIV group, 17 in the TIV-1 group and 13 in the TIV-2 group) were eliminated from the ATP cohort for analysis of immunogenicity due to protocol violation on inclusion or exclusion criteria, administration of any medication forbidden by the protocol, non-compliance with blood sampling schedule or essential serological data missing.

No deviations from specifications for age were observed. Deviations from specifications for intervals between study visits were observed for most of the subjects having the phone contact on Day 180.

3.1.3 Evaluation of Immunogenicity and Results

The analysis of immunogenicity was performed on the ATP cohort for immunogenicity

3.1.3.1 Lot-to Lot-Consistency for the Three QIV Lots

The limits of the two-sided 95% CI for the largest GMT ratios among the 3 lots of D-QIV were between 0.67 and 1.5 for the four strains. Therefore, the criteria for lot-to-lot consistency were met for the 3 considered lots of D-QIV.

The results of the inferential analysis of the between-group comparisons are presented in table 10 for the four strains (A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage) and B/Brisbane/3/2007 (Yamagata lineage)).

Table 10: Adjusted GMT ratios of HI antibody at Day 21 for the maximum difference among two lots of D-QIV for the four strains (ATP cohort)

Formulation (Strain)	Lots				Adjusted GMT ratio (D-QIV-1/D-QIV2)		
	D-QIV-1		D-QIV-2			95% CI	
	N	Adjusted GMT	N	Adjusted GMT	Value	LL	UL
A/California/7/2009 (H1N1)	600	196.5	599	209.1	0.95	0.80	1.11
A/Victoria/210/2009 (H3N2)	600	306.8	599	330.6	0.92	0.81	1.04
B/Brisbane/60/2008 (Victoria)	600	410.7	599	396.7	1.14	1.03	1.21
B/Brisbane/3/2007 (Yamagata)	600	605	599	599	1.00	0.90	1.13

N = Number of subjects with both pre- and post-vaccination results available
D-QIV-1 = Subjects received FLU D-QIV in Lot 1
D-QIV-2 = Subjects received FLU D-QIV in Lot 2
Adjusted GMT = geometric mean antibody titer adjusted for baseline titer

Reviewer's comment: *The point estimate and the CI of the GMT obtained by the reviewer is slightly different from what is reported by the applicant for B/Brisbane/60/2008 (Victoria lineage) strain (applicant reported a 1.04 GMT value with 95% CI [0.93, 1.15])*

3.1.3.2 Non-Inferiority of D-QIV versus TIV

The pre-specified criteria for non-inferiority of D-QIV versus TIV in terms of adjusted GMT ratio and SCR difference were met for all 4 strains shared with the TIVs (TIV-1 and TIV2).

The upper limit of the two 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 (H1N1) and **1.07** for A/Victoria (H3N2), which both did not exceed the pre-specified upper limit criterion 1.5.

The upper limit of the two sided 95% CI for the adjusted GMT ratio of TIV-1 over D-QIV for the B/Victoria strain was **1.07**, which did not exceed the pre-specified upper limit criterion 1.5.

The upper limit of the two sided 95% CI for the adjusted GMT ratio of TIV-2 over D-QIV for the B/Yamagata strain was **1.07**, which did not exceed the pre-specified upper limit criterion 1.5.

Table 11 presents the results of non-inferiority analysis of the D-QIV versus TIV GMTs for all four strains

Table 11: Non-inferiority of D-QIV versus TIV in terms of GMTs (adjusted GMT ratio) at Day 21 (ATP cohort for immunogenicity)

Anti-body	TIV		D-QIV		Adjusted GMT ratio (TIV[1]/D-QIV)		
						95% CI	
	N	Adjusted GMT	N	Adjusted GMT	Value	LL	UL
A/California/7/2009 (H1N1) (1/DIL)	1135	214.6	1801	201.3	1.07	0.96	1.18
A/Victoria/210/2009(H3N2) (1/DIL)	1135	312.2	1801	318.5	0.98	0.90	1.07
B/Brisbane/60/2008 (Victoria lineage)	605	395.3	1801	404.2	0.98	0.90	1.07
B/Brisbane/3/2007 (Yamagata lineage)	530	584.7	1801	600.8	0.97	0.89	1.07

[1]TIV = subjects received either TIV-1 or TIV-2 for the 2 A strains (A/California/7/2009 (H1N1) & A/Victoria/210/2009(H3N2))
= subjects received TIV-1 for the B/Brisbane/60/2008 (Victoria lineage) and
= subjects received TIV-2 for the B/Brisbane/3/2007 (Yamagata lineage)

The upper limit of the two-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 (H1N1), A/Victoria (H3N2) respectively, which did not exceed the pre-specified upper limit criterion 10%.

The upper limit of the two-sided 95% CI for the difference in SCR of TIV-1 minus D-QIV for the B/Victoria strain was **1.83%**, which did not exceed the pre-specified upper limit criterion 10%.
The upper limit of the two-sided 95% CI for the difference in SCR of TIV-2 minus D-QIV for the B/Yamagata strain was **2.01%**, which did not exceed the pre-specified upper limit criterion 10%.

Seroconversion and vaccine responses are defined as follows:

- S- = seronegative subjects (antibody titer < 101/DIL) prior to vaccination

S+ = seropositive subjects (antibody titer ≥ 101/DIL) prior to vaccination

Vaccine response defined as:
For initially seronegative subjects: post-vaccination antibody titer ≥ 40 1/DIL at PI(D21)
For initially seropositive subjects: antibody titer at PI(D21) ≥ 4 fold the pre-vaccination antibody titer

Table 12 presents the results of non-inferiority analysis of the D-QIV versus TIV SCRs at day 21 for all four strains

Table 12: Non-inferiority of D-QIV versus TIV-2 in terms of seroconversion rate (difference in seroconversion rate) at Day 21 for the four strains.

[1]TIV = subjects received either TIV-1 or TIV-2 for the 2 A strains (A/California/7/2009 (H1N1) & A/Victoria/210/2009(H3N2))

Anti-body	Pre-vaccination status	TIV			D-QIV			Difference in vaccine response rate (TIV[1] minus D-QIV)		
									95% CI	
		N	n	%	N	n	%	%	LL	UL
A/California/7/2009 (H1N1) (1/DIL)	Total	1135	892	78.6	1801	1396	77.5	1.08	-2.03	4.11
A/Victoria/210/2009 (H3N2) (1/DIL)	Total	1135	769	67.8	1801	1287	71.5	-3.71	-7.15	-0.30
B/Brisbane/60/2008 (Victoria lineage)	Total	605	335	55.4	1801	1046	58.1	-2.71	-7.29	1.83
B/Brisbane/3/2007 (Yamagata lineage)	Total	530	313	59.1	1801	1112	61.7	-2.69	-7.47	2.01

= subjects received TIV-1 for the B/Brisbane/60/2008 (Victoria lineage) and
= subjects received TIV-2 for the B/Brisbane/3/2007 (Yamagata lineage)
N = number of subjects with pre and post-vaccination results available
n/% = number/percentage of subjects with a vaccine response

3.1.3.3 Superiority of D-QIV versus TIV

The results of the superiority analysis of D-QIV versus TIV are presented in tables 13 and 14 in terms of GMTs and in tables 15 and 16 in terms of SCRs.

The pre-specified criteria for superiority of D-QIV versus TIVs in terms of adjusted GMT ratio and SCR difference were met for both B-strains that were not in the respective TIV.

- The lower limit of the two sided 95% CI for the adjusted GMT ratio of D-QIV over TIV-2 for the B/Victoria strain was **1.42**, which is greater than the pre-specified criterion 1.
- The lower limit of the two sided 95% CI for the adjusted GMT ratio of D-QIV over TIV-1 for the B/Yamagata strain was **1.41** which is greater than the pre-specified criterion 1.

- The lower limit of the two-sided 95% CI for the difference in SCR of D-QIV minus TIV-2 for the B/Victoria strain was **5.70%**, which is greater than the pre-specified criterion 0%.
- The lower limit of the two-sided 95% CI for the difference in SCR of D-QIV minus TIV-1 for the B/Yamagata strain was **11.54%**, which is greater than the pre-specified criterion 0%.

Table 13: Superiority of D-QIV versus TIV-2 in terms of GMT ratio at Day 21 for the B/Brisbane/60/2008 (Victoria lineage) strain.

D-QIV		TIV-2		Adjusted GMT ratio (D-QIV/TIV-2)		
					95% CI	
N	Adjusted GMT	N	Adjusted GMT	Value	LL	UL
1801	403.5	530	259.3	1.56	1.42	1.71

Table 14: Superiority of D-QIV versus TIV-1 in terms of GMT ratio at Day 21 for the B/Brisbane/3/2007 (Yamagata lineage) strain.

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

Table 15: Superiority of D-QIV versus TIV-2 in terms of SCR (difference in SCR) at Day 21 for the B/Brisbane/60/2008 (Victoria lineage) strain.

D-QIV			TIV-2			Difference in Vaccine response rate (D-QIV minus TIV-2)		
							95% CI	
N	n	%	N	n	%	%	LL	UL
1801	1046	58.1	530	252	47.5	10.53	5.70	15.33

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with a vaccine response

Table 16: Superiority of D-QIV versus TIV-1 in terms of SCR (difference in SCR) at Day 21 for the B/Brisbane/3/2007 (Yamagata lineage) strain.

D-QIV			TIV-1			Difference in Vaccine response rate (D-QIV minus TIV-1)		
							95% CI	
N	n	%	N	n	%	%	LL	UL
1801	1112	61.7	605	276	45.6	16.12	11.54	20.65

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with a vaccine response

3.1.3.4 Descriptive and Sub-group Analysis of Immunogenicity

3.1.3.4.1 Descriptive Analysis: Immunogenicity Results

Geometric Mean Titers and Seropositivity Rates

The GMTs and seropositivity rates with 95% CIs on Day 0 and Day 21 for HI antibodies against the 4 strains in each group are presented in table 17.

Point estimates for the post vaccination GMTs for each strain and each group is in bold face and highlighted in the table.

Table 17: Seropositivity rates and GMTs for HI antibodies at Day 0 and Day 21

				>= 10 1/DIL				GMT		
						95% CI			95% CI	
Strain	Group	Timing	N	n	%	LL	UL	value	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

N = number of subjects with available results
n/% = number/percentage of subjects with titer within the specified range
PRE= visit 1 Day 0,
PI(D21)= visit 2 Day 21

Seroconversion Rates

The seroconversion rates for HI antibodies against the 4 strains in each group on Day 21 are shown in table 18.
Point estimates for the SCRs for each strain in all groups are displayed in bold faces.

Table 18: Seroconversion rate (SCR) for HI antibodies against the four strains at visit 2 Day 21

Strain	Group	N	n	%	SCR	
					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

*TIV-2 did not contain B/Brisbane/60/2008 strain (Victoria lineage)
**TIV-1 did not contain B/Brisbane/3/2007 strain (Yamagata lineage)
Seroconversion defined as:
For initially seronegative subjects, antibody titer >= 40 1/DIL after vaccination
For initially seropositive subjects, antibody titer after vaccination >= 4 fold the pre-vaccination antibody titer
N = Number of subjects with pre- and post-vaccination results available
n/% = Number/percentage of seroconverted subjects

Seroprotection Rates

The seroprotection rates for HI antibodies against the 4 strains in each group on Day 0 and Day 21 are provided in table 19.

Post vaccination SPR point estimates are described in bold faces and highlighted in the table.

Mean Geometric Increase (MGI)

The MGI for HI antibodies against the 4 strains in each group on visit 2 (Day 21) are shown in table 20.

Point estimates for the MGIs against the four strains for each group are highlighted with bold faces in the table.

Table 19: Seroprotection rates for HI antibodies at Day 0 and Day 21

Strain	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	97.3
	TIV-2	PRE	530	285	53.8	49.4	58.1
		PI(D21)	534	517	96.8	95	98.1
B/Brisbane/60/2008 (Victoria)	D-QIV	PRE	1801	1423	79	77.1	80.9
		PI(D21)	1809	1788	98.8	98.2	99.3
	TIV-1	PRE	605	477	78.8	75.4	82
		PI(D21)	608	599	98.5	97.2	99.3
	TIV-2	PRE	530	412	77.7	74	81.2
		PI(D21)	534	513	96.1	94.1	97.5
B/Brisbane/3/2007 (Yamagata)	D-QIV	PRE	1801	1494	83	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

PRE= visit 1 Day 0, PI(D21)= visit 2 Day 21

Table 20: Mean geometric increase (MGI) for HI antibodies against the 4 strains at day 21

Strain	Group	N	MGI		
			Value	95% CI	
				LL	UL
A/California/7/2009 (H1N1) (1/DIL)	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) (1/DIL)	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) (1/DIL)	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) (1/DIL)	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 titer to the Day 0 reciprocal HI titer

Immunogenicity analysis results by age, gender, region and ethnicity are provided in the following subsections

3.1.3.4.2 Immunogenicity Results by Age Strata

Immunogenicity results for the age strata (18-60 years old and ≥61 years old) are presented in tables 21 -23 for SCR, for seropositivity rates and GMTs, and for SPR, respectively.

Table 21: Seroconversion rate (SCR) for HI antibodies against the four strains at visit 1 (Day 0) and visit 2 (Day 21) by age strata

Strain	Group	Sub-group (Age in Years)	N		SCR		
				n	%	95% CI	
						LL	UL
A/California/7/2009 (H1N1)	D-QIV	18-60	825	685	83.0	80.3	85.5
		≥61	976	711	72.8	69.9	75.6
	TIV-1	18-60	277	225	81.2	76.1	85.7
		≥61	328	242	73.8	68.7	78.5
	TIV-2	18-60	240	196	81.7	76.2	86.4
		≥61	290	229	79.0	73.8	83.5
A/Victoria/210/2009 (H3N2)	D-QIV	18-60	825	646	78.3	75.3	81.1
		≥61	976	641	65.7	62.6	68.7
	TIV-1	18-60	277	204	73.6	68.0	78.7
		≥61	328	194	59.1	53.6	64.5
	TIV-2	18-60	240	177	73.8	67.7	79.2
		≥61	290	194	66.9	61.2	72.3
B/Brisbane/60/2008 (Victoria)	D-QIV	18-60	825	560	67.9	64.6	71.1
		≥61	976	486	49.8	46.6	53.0
	TIV-1	18-60	277	184	66.4	60.5	72.0
		≥61	328	151	46.0	40.5	51.6
	TIV-2	18-60	240	124	51.7	45.1	58.1
		≥61	290	128	44.1	38.3	50.1
B/Brisbane/3/2007 (Yamagata)	D-QIV	18-60	825	553	67.0	63.7	70.2
		≥61	976	559	57.3	54.1	60.4
	TIV-1	18-60	277	142	51.3	45.2	57.3
		≥61	328	134	40.9	35.5	46.4
	TIV-2	18-60	240	146	60.8	54.3	67.0
		≥61	290	167	57.6	51.7	63.3

Seroconversion defined as:
For initially seronegative subjects, antibody titer ≥ 40 1/DIL after vaccination
For initially seropositive subjects, antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer
N = Number of subjects with pre- and post-vaccination results available,
n/% = Number/percentage of seroconverted subjects

Reviewer's comment

*The descriptive analysis of the SCR shows a relatively higher SCR rate in the age group of 18-60 years compared to the age group 60 years and older for all three groups(D-QIV, TIV-1 and TIV-2) and all fours strains (for example **67.9%** of the subjects in the age group 18-60 were seroconverted compared to **49.8%** on the >60 years age group for the D-QIV group and B/Brisbane/60/2008 (Victoria) strain) . But the values for both age groups appear to be similar with the overall point estimates for SCR (presented on table 18 above).*

No inferential analysis has conducted to show if any of the differences are statistically significant

Table 22: Seropositivity rates and GMTs for HI antibodies at day 0 and day 21 by age

Strain	Group	Sub- group (Age in years)	Timing	N	≥ 10 1/DIL				GMT		
					n	%	95% CI		Value	95% CI	
							LL	UL		LL	UL
A/California/7/2009 (H1N1)	D-QIV	18-60	PRE	825	404	49.0	45.5	52.4	15.3	13.9	16.9
			PI(D21)	827	802	97.0	95.6	98.0	**314.3**	286.3	645.0
		≥ 61	PRE	976	563	57.7	54.5	60.8	14.2	13.2	15.2
			PI(D21)	982	936	95.3	93.8	96.6	**138.1**	126.3	151.0
	TIV-1	18-60	PRE	277	153	55.2	49.2	61.2	17	14.5	20.1
			PI(D21)	278	271	97.5	94.9	99	**338.9**	287.6	399.3
		≥ 61	PRE	328	199	60.7	55.2	66	14.6	12.8	16.6
			PI(D21)	330	315	95.5	92.3	97.4	**150.8**	129	176.3
	TIV-2	18-60	PRE	240	124	51.7	45.1	58.1	16.2	13.5	19.3
			PI(D21)	244	238	97.5	94.7	99.1	**313.3**	262.9	373.3
		≥ 61	PRE	290	167	57.6	51.7	63.3	13	11.4	14.9
			PI(D21)	290	276	95.2	92	97.3	**154**	129.4	183.3
A/Victoria/210/2009(H3N2)	D-QIV	18-60	PRE	825	596	72.2	69.1	75.3	28.1	25.4	31
			PI(D21)	827	817	98.8	97.8	99.4	**372.5**	342.9	404.6
		≥ 61	PRE	976	820	84	81.6	86.3	39.9	36.5	43.6
			PI(D21)	982	966	98.4	97.4	99.1	**273**	251.7	296
	TIV-1	18-60	PRE	277	207	74.7	69.2	79.7	32.9	27.8	39.1
			PI(D21)	278	272	97.8	95.4	99.2	**349.2**	299.1	407.6
		≥ 61	PRE	328	281	85.7	81.4	89.3	43.2	37.2	50.1
			PI(D21)	330	322	97.6	95.3	98.9	**261**	226.2	301.2
	TIV-2	18-60	PRE	240	177	73.8	67.7	79.2	30.7	25.4	37.3
			PI(D21)	244	239	98	95.3	99.3	**340.6**	288.2	402.5
		≥ 61	PRE	290	248	85.5	80.9	89.4	40.3	34.4	47.2
			PI(D21)	290	289	99.7	98.1	100	**340.3**	292.2	396.4
B/Brisbane/60/2008 (Victoria lineage)	D-QIV	18-60	PRE	825	666	80.7	77.9	83.4	60.4	54.4	67.1
			PI(D21)	827	819	99	98.1	99.6	**497**	463.6	532.8
		≥ 61	PRE	976	875	89.7	87.6	91.5	87.4	80.6	94.9
			PI(D21)	982	976	99.4	98.7	99.8	**340.3**	321.1	360.5
	TIV-1	18-60	PRE	277	216	78.0	72.6	82.7	57.7	48.0	69.4
			PI(D21)	278	276	99.3	97.4	99.9	**495.0**	442.3	554.1
		≥ 61	PRE	328	295	89.9	86.2	93.0	90.4	78.1	104.7
			PI(D21)	330	325	98.5	96.5	99.5	**324.7**	289.5	364.2
	TIV-2	18-60	PRE	240	199	82.9	77.5	87.5	63.1	52.4	76.0
			PI(D21)	244	236	96.7	93.6	98.6	**256.0**	222.4	294.7
		≥ 61	PRE	290	253	87.2	82.8	90.9	79.6	67.7	93.7
			PI(D21)	290	282	97.2	94.6	98.8	**260.6**	227.8	298.0
B/Brisbane/3/2007(Yamagata lineage)	D-QIV	18-60	PRE	825	683	82.8	80.0	85.3	97.6	86.9	109.5
			PI(D21)	827	820	99.2	98.3	99.7	**772.8**	719.7	829.8
		≥ 61	PRE	976	871	89.2	87.1	91.1	104.8	96.1	114.2
			PI(D21)	982	974	99.2	98.4	99.6	**487.5**	457.6	519.2
	TIV-1	18-60	PRE	277	227	81.9	76.9	86.3	89.8	73.7	109.3
			PI(D21)	278	272	97.8	95.4	99.2	**459.9**	395.3	535.1
		≥ 61	PRE	328	298	90.9	87.2	93.7	111.3	95.7	129.5
			PI(D21)	330	325	98.5	96.5	99.5	**334.0**	296.6	376.2
	TIV-2	18-60	PRE	240	202	84.2	78.9	88.5	101.0	82.3	124.0
			PI(D21)	244	242	99.2	97.1	99.9	**671.7**	591.0	763.3
		≥ 61	PRE	290	255	87.9	83.6	91.4	98.7	83.7	116.5
			PI(D21)	290	290	100	98.7	100	**516.7**	460.8	579.5

Table 23: Seroprotection rates for HI antibodies at day 0 and day 21 by age strata

Strain	Group	Sub-group (Age in	Timing	N	SPR			
							95% CI	
					n	%	LL	UL
A/California/7/2009 (H1N1)	D-QIV	18-60	PRE	825	263	31.9	28.7	35.2
			PI(D21)	827	788	95.3	93.6	96.6
		≥ 61	PRE	976	251	25.7	23.0	28.6
			PI(D21)	982	863	87.9	85.7	89.9
	TIV-1	18-60	PRE	277	92	33.2	27.7	39.1
			PI(D21)	278	265	95.3	92.1	97.5
		≥ 61	PRE	328	75	22.9	18.4	27.8
			PI(D21)	330	293	88.8	84.9	92.0
	TIV-2	18-60	PRE	240	79	32.9	27.0	39.3
			PI(D21)	244	234	95.9	92.6	98.0
		≥ 61	PRE	290	60	20.7	16.2	25.8
			PI(D21)	290	261	90.0	86.0	93.2
A/Victoria/210/2009 (H3N2)	D-QIV	18-60	PRE	825	398	48.2	44.8	51.7
			PI(D21)	827	810	97.9	96.7	98.8
		≥ 61	PRE	976	567	58.1	54.9	61.2
			PI(D21)	982	941	95.8	94.4	97.0
	TIV-1	18-60	PRE	277	155	56.0	49.9	61.9
			PI(D21)	278	269	96.8	93.9	98.5
		≥ 61	PRE	328	198	60.4	54.8	65.7
			PI(D21)	330	314	95.2	92.2	97.2
	TIV-2	18-60	PRE	240	117	48.8	42.3	55.3
			PI(D21)	244	234	95.9	92.6	98.0
		≥ 61	PRE	290	168	57.9	52.0	63.7
			PI(D21)	290	283	97.6	95.1	99.0
B/Brisbane/60/2008 (Victoria)	D-QIV	18-60	PRE	825	599	72.6	69.4	75.6
			PI(D21)	827	816	98.7	97.6	99.3
		≥ 61	PRE	976	824	84.4	82.0	86.6
			PI(D21)	982	972	99.0	98.1	99.5
	TIV-1	18-60	PRE	277	200	72.2	66.5	77.4
			PI(D21)	278	276	99.3	97.4	99.9
		≥ 61	PRE	328	277	84.5	80.1	88.2
			PI(D21)	330	323	97.9	95.7	99.1
	TIV-2	18-60	PRE	240	178	74.2	68.1	79.6
			PI(D21)	244	236	96.7	93.6	98.6
		≥ 61	PRE	290	234	80.7	75.7	85.1
			PI(D21)	290	277	95.5	92.5	97.6
B/Brisbane/3/2007 (Yamagata)	D-QIV	18-60	PRE	825	649	78.7	75.7	81.4
			PI(D21)	827	820	99.2	98.3	99.7
		≥ 61	PRE	976	845	86.6	84.3	88.7
			PI(D21)	982	972	99.0	98.1	99.5
	TIV-1	18-60	PRE	277	213	76.9	71.5	81.7
			PI(D21)	278	270	97.1	94.4	98.7
		≥ 61	PRE	328	284	86.6	82.4	90.1
			PI(D21)	330	325	98.5	96.5	99.5
	TIV-2	18-60	PRE	240	197	82.1	76.6	86.7
			PI(D21)	244	242	99.2	97.1	99.9
		≥ 61	PRE	290	244	84.1	79.4	88.1
			PI(D21)	290	290	100	98.7	100

SPR is defined as the percentage of vaccinees with a serum HI titer ≥ 1:40

Reviewer's comment

The descriptive analysis of the seropositivity rates and GMT show:

- *Similar results in seropositivity rates in both age groups*
- *Higher GMT values in the age group of 18-60 years compared to the age group 60 years and older for all three groups and all fours strains, but there is a difference in the number of subjects with available results (N) in both groups as well. Post vaccination point estimate GMT values are shown in bold blue color for age group 18-60 and bold green for age group >60 in the table. No inferential analysis has conducted to show if the difference is statistically significant.*

The descriptive analysis of the seroprotection rates shows similar results in both age groups.

3.1.3.4.3 Immunogenicity results by Gender

Immunogenicity results by gender for seropositivity rates and GMTs, for SCR, and for SPR are summarized on tables 24 -26

Table 24: Seropositivity rates and GMTs for HI antibodies against the 4 strains at Day 0 and Day 21 by gender

Strain	Group	Sub-group (Gender)	Timing	N	>= 10 1/DIL				GMT		
							95% CI			95% CI	
					n	%	LL	UL	value	LL	UL
A/California/7/2009 (H1N1)	D-QIV	Male	PRE	765	422	55.2	51.6	58.7	15.3	13.9	16.7
			PI(D21)	770	742	96.4	94.8	97.6	176.2	159.3	194.9
		Female	PRE	1036	545	52.6	49.5	55.7	14.3	13.2	15.4
			PI(D21)	1039	996	95.9	94.5	97.0	221.9	202.9	242.6
	TIV-1	Male	PRE	280	162	57.9	51.8	63.7	15.6	13.4	18.1
			PI(D21)	280	270	96.4	93.5	98.3	198.2	166.7	235.6
		Female	PRE	325	190	58.5	52.9	63.9	15.7	13.6	18.1
			PI(D21)	328	316	96.3	93.7	98.1	237.3	202.2	278.5
	TIV-2	Male	PRE	226	127	56.2	49.5	62.8	14.9	12.6	17.7
			PI(D21)	229	220	96.1	92.7	98.2	219.2	178.5	269.1
		Female	PRE	304	164	53.9	48.2	59.7	14.0	12.1	16.1
			PI(D21)	305	294	96.4	93.6	98.2	208.5	177.4	245.1
A/Victoria/210/2009 (H3N2)	D-QIV	Male	PRE	765	620	81.0	78.1	83.8	35.1	31.8	38.7
			PI(D21)	770	758	98.4	97.3	99.2	273.2	249.7	299.0
		Female	PRE	1036	796	76.8	74.1	79.4	33.2	30.3	36.3
			PI(D21)	1039	1025	98.7	97.7	99.3	349.3	323.8	377.0
	TIV-1	Male	PRE	280	238	85.0	80.3	89.0	41.5	35.4	48.5
			PI(D21)	280	275	98.2	95.9	99.4	300.1	257.3	349.9
		Female	PRE	325	250	76.9	72.0	81.4	35.5	30.2	41.7
			PI(D21)	328	319	97.3	94.9	98.7	296.6	256.4	343.0
	TIV-2	Male	PRE	226	185	81.9	76.2	86.7	40.0	33.0	48.5

Strain	Group	Sub-group (Gender)	Timing	N	>= 10 1/DIL				GMT		
							95% CI			95% CI	
					n	%	LL	UL	value	LL	UL
			PI(D21)	229	228	99.6	97.6	100	337.6	286.3	398.2
		Female	PRE	304	240	78.9	73.9	83.4	32.8	27.9	38.4
			PI(D21)	305	300	98.4	96.2	99.5	342.6	293.9	399.3
B/Brisbane/60/2008 (Victoria)	D-QIV	Male	PRE	765	667	87.2	84.6	89.5	82.3	74.5	90.9
			PI(D21)	770	765	99.4	98.5	99.8	411.9	384.8	441.0
		Female	PRE	1036	874	84.4	82.0	86.5	68.1	62.4	74.4
			PI(D21)	1039	1030	99.1	98.4	99.6	399.3	375.6	424.4
	TIV-1	Male	PRE	280	245	87.5	83.0	91.1	87.6	74.0	103.6
			PI(D21)	280	279	99.6	98.0	100	417.0	373.5	465.7
		Female	PRE	325	266	81.8	77.2	85.9	63.4	53.9	74.6
			PI(D21)	328	322	98.2	96.1	99.3	375	332.4	422.9
	TIV-2	Male	PRE	226	202	89.4	84.6	93.1	85.2	71.4	101.6
			PI(D21)	229	224	97.8	95.0	99.3	286.5	248.9	329.8
		Female	PRE	304	250	82.2	77.5	86.4	63.0	53.3	74.5
			PI(D21)	305	294	96.4	93.6	98.2	239.2	209.5	273.2
B/Brisbane/3/2007 (Yamagata)	D-QIV	Male	PRE	765	675	88.2	85.7	90.4	108.5	97.8	120.3
			PI(D21)	770	766	99.5	98.7	99.9	583.5	541.8	628.3
		Female	PRE	1036	879	84.8	82.5	87.0	96.5	87.7	106.2
			PI(D21)	1039	1028	98.9	98.1	99.5	615.7	577.5	656.4
	TIV-1	Male	PRE	280	251	89.6	85.5	93.0	118.0	99.7	139.7
			PI(D21)	280	278	99.3	97.4	99.9	420.4	370.5	477.1
		Female	PRE	325	274	84.3	79.9	88.1	88.1	74.1	104.8
			PI(D21)	328	319	97.3	94.9	98.7	360.0	313.0	414.0
	TIV-2	Male	PRE	226	201	88.9	84.1	92.7	110.6	91.7	133.3
			PI(D21)	229	229	100	98.4	100	593.4	521.0	675.7
		Female	PRE	304	256	84.2	79.6	88.1	92.4	77.3	110.4
			PI(D21)	305	303	99.3	97.7	99.9	574.5	512.1	644.5

PRE= visit 1 Day 0, PI(D21)= visit 2 Day 21
N = number of subjects with available results
n/% = number/percentage of subjects with titer within the specified range

Reviewer's comment

The descriptive analysis shows:

- *Similar results in seropositivity rates for both sub-groups (males and females).*
- *The number of subjects with available results were different in the male and female sub-groups, so is the GMT value for both. (There were 57% females vs. 43% males in the D-QIV, 54% females vs. 46% males in TIV-1, and 57% females vs. 43% males in the TIV-2 group)*

Table 25: Seroconversion rate for HI antibodies against the 4 strains at day 21 by gender

Strain	Group	Sub-group (Gender)	N	SCR			
				n	%	95% CI	
						LL	UL
A/California/7/2009 (H1N1)	D-QIV	Male	765	572	74.8	71.5	77.8
		Female	1036	824	79.5	76.9	82.0
	TIV-1	Male	280	209	74.6	69.1	79.6
		Female	325	258	79.4	74.6	83.7
	TIV-2	Male	226	180	79.6	73.8	84.7
		Female	304	245	80.6	75.7	84.9
A/Victoria/210/2009 (H3N2)	D-QIV	Male	765	527	68.9	65.5	72.2
		Female	1036	760	73.4	70.6	76.0
	TIV-1	Male	280	179	63.9	58.0	69.6
		Female	325	219	67.4	62.0	72.5
	TIV-2	Male	226	147	65.0	58.4	71.2
		Female	304	224	73.7	68.4	78.5
B/Brisbane/60/2008 (Victoria)	D-QIV	Male	765	414	54.1	50.5	57.7
		Female	1036	632	61.0	58.0	64.0
	TIV-1	Male	280	140	50.0	44.0	56.0
		Female	325	195	60.0	54.4	65.4
	TIV-2	Male	226	100	44.2	37.7	51.0
		Female	304	152	50.0	44.2	55.8
B/Brisbane/3/2007 (Yamagata)	D-QIV	Male	765	449	58.7	55.1	62.2
		Female	1036	663	64.0	61.0	66.9
	TIV-1	Male	280	123	43.9	38.0	50.0
		Female	325	153	47.1	41.5	52.7
	TIV-2	Male	226	130	57.5	50.8	64.1
		Female	304	183	60.2	54.5	65.7

Seroconversion defined as:

For initially seronegative subjects, antibody titer >= 40 1/DIL after vaccination

For initially seropositive subjects, antibody titer after vaccination >= 4 fold the pre-vaccination antibody titer

N = Number of subjects with pre- and post-vaccination results available

n/% = Number/percentage of seroconverted subjects

Reviewer's comment

Similar percentage of seroconverted subjects has been observed for both males and females. The largest difference observed was for the B/Brisbane/60/2008 (Victoria lineage) strain for the TiV-1 group (50% SCR for males vs. 60% for females). No inferential analysis has been conducted to check if any difference is statistical significant.

Table 26: Seroprotection rates and GMTs for HI antibodies at Day 0 and Day 21 by gender

Strain	Group	Sub-group	Timing	N	SPR			
					n	%	95% CI	
							LL	UL
A/California/7/2009 (H1N1)	D-QIV	Male	PRE	765	223	29.2	26.0	32.5
			PI(D21)	770	696	90.4	88.1	92.4
		Female	PRE	1036	291	28.1	25.4	30.9
			PI(D21)	1039	955	91.9	90.1	93.5
	TIV-1	Male	PRE	280	78	27.9	22.7	33.5
			PI(D21)	280	256	91.4	87.5	94.4
		Female	PRE	325	89	27.4	22.6	32.6
			PI(D21)	328	302	92.1	88.6	94.8
	TIV-2	Male	PRE	226	62	27.4	21.7	33.7
			PI(D21)	229	212	92.6	88.4	95.6
		Female	PRE	304	77	25.3	20.5	30.6
			PI(D21)	305	283	92.8	89.3	95.4
A/Victoria/210/2009 (H3N2)	D-QIV	Male	PRE	765	419	54.8	51.2	58.3
			PI(D21)	770	741	96.2	94.6	97.5
		Female	PRE	1036	546	52.7	49.6	55.8
			PI(D21)	1039	1010	97.2	96.0	98.1
	TIV-1	Male	PRE	280	172	61.4	55.5	67.2
			PI(D21)	280	269	96.1	93.1	98.0
		Female	PRE	325	181	55.7	50.1	61.2
			PI(D21)	328	314	95.7	92.9	97.6
	TIV-2	Male	PRE	226	130	57.5	50.8	64.1
			PI(D21)	229	223	97.4	94.4	99.0
		Female	PRE	304	155	51.0	45.2	56.7
			PI(D21)	305	294	96.4	93.6	98.2
B/Brisbane/60/2008 (Victoria)	D-QIV	Male	PRE	765	619	80.9	77.9	83.6
			PI(D21)	770	764	99.2	98.3	99.7
		Female	PRE	1036	804	77.6	74.9	80.1
			PI(D21)	1039	1024	98.6	97.6	99.2
	TIV-1	Male	PRE	280	231	82.5	77.5	86.8
			PI(D21)	280	279	99.6	98.0	100
		Female	PRE	325	246	75.7	70.7	80.3
			PI(D21)	328	320	97.6	95.3	98.9
	TIV-2	Male	PRE	226	187	82.7	77.2	87.4
			PI(D21)	229	221	96.5	93.2	98.5
		Female	PRE	304	225	74.0	68.7	78.9
			PI(D21)	305	292	95.7	92.8	97.7
B/Brisbane/3/2007 (Yamagata)	D-QIV	Male	PRE	765	651	85.1	82.4	87.5
			PI(D21)	770	765	99.4	98.5	99.8
		Female	PRE	1036	843	81.4	78.9	83.7
			PI(D21)	1039	1027	98.8	98.0	99.4
	TIV-1	Male	PRE	280	242	86.4	81.9	90.2
			PI(D21)	280	277	98.9	96.9	99.8
		Female	PRE	325	255	78.5	73.6	82.8
			PI(D21)	328	318	97.0	94.5	98.5
		Male	PRE	226	193	85.4	80.1	89.7
			PI(D21)	229	229	100	98.4	100

Strain	Group	Sub-group	Timing	N	SPR			
					n	%	95% CI	
							LL	UL
		Female	PRE	304	248	81.6	76.8	85.8
	TIV-2		PI(D21)	305	303	99.3	97.7	99.9

N = Number of subjects with available results
n/% = Number/percentage of seroprotected subjects (HI titer >= 40 1/DIL)
PRE = Pre-vaccination, visit 1 (Day 0), PI(D21)= Post-vaccination, visit 2 (Day 21)

Reviewer's comment

The seroprotection rates are similar in both males and females.

3.1.3.4.4 Immunogenicity Results by Region

Demographic characteristics

Tables 27 and 28 present the summary of demographic characteristics by region for the TVC and ATP cohorts respectively.

Table 27: Summary of demographic characteristics by region (Total vaccinated cohort)

Characteristics	Parameters or Categories	US N = 1451		Europe N = 1973		Asia N =1232	
		Value or n	%	Value or n	%	Value or n	%
Age (in years) at vaccination dose: 1	Mean	57.7	-	59.6	-	55.6	-
	SD	18.29	-	16.74	-	18.41	-
	Median	64.0	-	65.0	-	65.0	-
	Minimum	18	-	18	-	18	-
	Maximum	92	-	91	-	92	-
Gender	Female	840	57.9	1107	56.1	689	55.9
	Male	611	42.1	866	43.9	543	44.1
Ethnicity	American Hispanic or Latino	188	13.0	18	0.9	0	0.0
	Not American Hispanic or Latino	1263	87.0	1955	99.1	1232	100
Geographic Ancestry	African heritage / African American	153	10.5	0	0.0	0	0.0
	American Indian or Alaskan native	7	0.5	4	0.2	0	0.0
	Asian - central/south Asian heritage	5	0.3	0	0.0	3	0.2
	Asian - east Asian heritage	1	0.1	0	0.0	1225	99.4
	Asian - Japanese heritage	0	0.0	0	0.0	1	0.1
	Asian - south east Asian heritage	0	0.0	0	0.0	2	0.2
	Native Hawaiian or other pacific islander	1	0.1	0	0.0	1	0.1
	White - Arabic / north African heritage	8	0.6	25	1.3	0	0.0
	White - Caucasian / European heritage	1258	86.7	1933	98.0	0	0.0
	Other	18	1.2	11	0.6	0	0.0

US= subjects from the United States
Europe = Subjects from Germany, Romania and Spain
Asia = Subjects from Korea and Taiwan
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Table 27: Summary of demographic characteristics by region (ATP cohort for immunogenicity sub-cohort)

Characteristics	Parameters or Categories	US N = 976		Europe N = 1072		Asia N = 903	
		Value or n	%	Value or n	%	Value or n	%
Age (years) at vaccination dose: 1	Mean	57.9	-	58.0	-	56.0	-
	SD	18.05	-	16.74	-	18.37	-
	Median	65.0	-	62.0	-	65.0	-
	Minimum	18	-	18	-	18	-
	Maximum	92	-	90	-	92	-
Gender	Female	556	57.0	610	56.9	506	56.0
	Male	420	43.0	462	43.1	397	44.0
Ethnicity	American Hispanic or Latino	114	11.7	10	0.9	0	0.0
	Not American Hispanic or Latino	862	88.3	1062	99.1	903	100
Geographic Ancestry	African heritage / African American	104	10.7	0	0.0	0	0.0
	American Indian or Alaskan native	5	0.5	1	0.1	0	0.0
	Asian - central/south Asian heritage	5	0.5	0	0.0	2	0.2
	Asian - east Asian heritage	1	0.1	0	0.0	898	99.4
	Asian - Japanese heritage	0	0.0	0	0.0	1	0.1
	Asian - south east Asian heritage	0	0.0	0	0.0	1	0.1
	Native Hawaiian or other pacific islander	1	0.1	0	0.0	1	0.1
	White - Arabic / north African heritage	5	0.5	15	1.4	0	0.0
	White - Caucasian / European heritage	843	86.4	1047	97.7	0	0.0
	Other	12	1.2	9	0.8	0	0.0

US= subjects from the United States
Europe = Subjects from Germany, Romania and Spain
Asia = Subjects from Korea and Taiwan
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Immunogenicity results by region

Immunogenicity results by region are provided in following tables (table 28 for seropositivity and GMT, table 29 for SCR, and table 30 for SPR)

Table 28: Seropositivity rates and GMTs for HI antibodies against each strain at day 0 and day 21 by region (ATP cohort for immunogenicity)

					≥ 10 1/DIL				GMT		
							95% CI			95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL
A/California/7/2009 (H1N1)	D-QIV	US	PRE	589	420	71.3	67.5	74.9	19.8	17.9	21.8
			PI(D21)	593	587	99	97.8	99.6	249.3	223.3	278.3
		Europe	PRE	655	290	44.3	40.4	48.2	12	10.9	13.1
			PI(D21)	659	607	92.1	89.8	94.1	178.2	157.7	201.4
		Asia	PRE	557	257	46.1	41.9	50.4	13.7	12.2	15.3
			PI(D21)	557	544	97.7	96	98.8	184.6	165.1	206.4
	TIV-1	US	PRE	198	142	71.7	64.9	77.9	21.2	17.5	25.6
			PI(D21)	200	200	100	98.2	100	306.4	250.9	374.3
		Europe	PRE	219	105	47.9	41.2	54.8	11.7	10.1	13.7
			PI(D21)	220	205	93.2	89	96.1	174.5	141.9	214.5
		Asia	PRE	188	105	55.9	48.4	63.1	15.9	13.2	19.2
			PI(D21)	188	181	96.3	92.5	98.5	198.1	163.1	240.8
	TIV-2	US	PRE	183	126	68.9	61.6	75.5	18.9	15.7	22.7
			PI(D21)	183	181	98.9	96.1	99.9	255.9	208.3	314.3
		Europe	PRE	189	86	45.5	38.3	52.9	10.9	9.3	12.7
			PI(D21)	193	183	94.8	90.7	97.5	195.3	157.2	242.7
		Asia	PRE	158	79	50	42	58	14.6	11.8	18.2
			PI(D21)	158	150	94.9	90.3	97.8	191.5	150.5	243.9
A/Victoria/210/2009 (H3N2)	D-QIV	US	PRE	589	474	80.5	77	83.6	35	31.2	39.4
			PI(D21)	593	583	98.3	96.9	99.2	322.6	289.2	360
		Europe	PRE	655	510	77.9	74.5	81	31.8	28.5	35.4
			PI(D21)	659	646	98	96.7	98.9	297.4	270.1	327.6
		Asia	PRE	557	432	77.6	73.9	81	35.6	31.5	40.1
			PI(D21)	557	554	99.5	98.4	99.9	327.5	297.2	360.8
	TIV-1	US	PRE	198	163	82.3	76.3	87.4	40.1	32.5	49.4
			PI(D21)	200	192	96	92.3	98.3	294.5	240.1	361.1
		Europe	PRE	219	166	75.8	69.6	81.3	30.8	25.7	36.9
			PI(D21)	220	215	97.7	94.8	99.3	248	208.5	294.9
		Asia	PRE	188	159	84.6	78.6	89.4	46.4	38.2	56.5
			PI(D21)	188	187	99.5	97.1	100	375	317.9	442.3
	TIV-2	US	PRE	183	150	82	75.6	87.2	43.5	35	54

					≥ 10 1/DIL				GMT		
							95% CI			95% CI	
Strain	Group	Sub-	Timing	N	n	%	LL	UL	value	LL	UL
			PI(D21)	183	181	98.9	96.1	99.9	347.1	282.1	427.2
		Europe	PRE	189	147	77.8	71.2	83.5	31.3	25.5	38.4
			PI(D21)	193	189	97.9	94.8	99.4	316.3	263.8	379.1
		Asia	PRE	158	128	81	74	86.8	33.1	26.7	41.1
			PI(D21)	158	158	100	97.7	100	364.2	299.1	443.3
	D-QIV	US	PRE	589	539	91.5	89	93.6	109	98.3	120.9
			PI(D21)	593	591	99.7	98.8	100	519.8	483.9	558.3
		Europe	PRE	655	569	86.9	84	89.4	75.4	67.6	84.1
			PI(D21)	659	655	99.4	98.5	99.8	418.4	389.7	449.3
		Asia	PRE	557	433	77.7	74.1	81.1	47.6	42.2	53.8
			PI(D21)	557	549	98.6	97.2	99.4	297.8	272.5	325.5
	TIV-1	US	PRE	198	178	89.9	84.8	93.7	101	83.3	122.4
			PI(D21)	200	198	99	96.4	99.9	524.4	456.4	602.4
		Europe	PRE	219	187	85.4	80	89.8	78.5	64.6	95.3
			PI(D21)	220	218	99.1	96.8	99.9	386.6	339.1	440.7
		Asia	PRE	188	146	77.7	71	83.4	49	39.6	60.7
			PI(D21)	188	185	98.4	95.4	99.7	296.7	255	345.2
B/Brisbane/60/2008 (Victoria)	TIV-2	US	PRE	183	164	89.6	84.3	93.6	97.2	80.4	117.6
			PI(D21)	183	181	98.9	96.1	99.9	365.4	320.5	416.5
		Europe	PRE	189	164	86.8	81.1	91.3	79.1	64.3	97.4
			PI(D21)	193	188	97.4	94.1	99.2	266.9	229.7	310.2
		Asia	PRE	158	124	78.5	71.2	84.6	44.7	35.6	56.2
			PI(D21)	158	149	94.3	89.5	97.4	166.5	135	205.2
	D-QIV	US	PRE	589	536	91	88.4	93.2	139.1	124.1	155.8
			PI(D21)	593	592	99.8	99.1	100	680.5	625.9	739.9
		Europe	PRE	655	539	82.3	79.1	85.1	87.9	77.5	99.6
			PI(D21)	659	648	98.3	97	99.2	594.1	547.3	644.9
		Asia	PRE	557	479	86	82.8	88.8	85.9	76.1	97.1
			PI(D21)	557	554	99.5	98.4	99.9	536	492.3	583.6
	TIV-1	US	PRE	198	184	92.9	88.4	96.1	146.1	120	177.8
			PI(D21)	200	200	100	98.2	100	537.2	460	627.5
B/Brisbane/3/2007(Yamagata)		Europe	PRE	219	177	80.8	75	85.8	84.4	68.1	104.4
			PI(D21)	220	213	96.8	93.6	98.7	347.6	294.5	410.3
		Asia	PRE	188	164	87.2	81.6	91.6	84.1	67.8	104.2
			PI(D21)	188	184	97.9	94.6	99.4	308.6	261.6	364
	TIV-2	US	PRE	183	167	91.3	86.2	94.9	125.2	102.9	152.4
			PI(D21)	183	183	100	98	100	673.6	582.6	778.7
		Europe	PRE	189	157	83.1	76.9	88.1	90	71.2	113.6
			PI(D21)	193	192	99.5	97.1	100	607.5	534.5	690.6
		Asia	PRE	158	133	84.2	77.5	89.5	86.8	68.1	110.6

					≥ 10 1/DIL				GMT		
							95% CI			95% CI	
Strain	Group	Sub-	Timing	N	n	%	LL	UL	value	LL	UL
			PI(D21)	158	157	99.4	96.5	100	467.7	392.5	557.3

US = Subjects from United States
Europe = Subjects from Germany, Romania and Spain
Asia = Subjects from Korea and Taiwan
N = number of subjects with available results
n/% = number/percentage of subjects with titer within the specified range
PRE= visit 1 Day 0, PI(D21)= visit 2 Day 21

Table 29: Seroconversion rate for HI antibodies against each strain at day 21 by region (ATP cohort for immunogenicity)

				SCR			
						95% CI	
Strain	Group	Sub-group	N	n	%	LL	UL
A/California/7/2009 (H1N1)	D-QIV	US	589	463	78.6	75.1	81.9
		Europe	655	508	77.6	74.2	80.7
		Asia	557	425	76.3	72.5	79.8
	TIV-1	US	198	152	76.8	70.3	82.5
		Europe	219	174	79.5	73.5	84.6
		Asia	188	141	75.0	68.2	81.0
	TIV-2	US	183	144	78.7	72.0	84.4
		Europe	189	162	85.7	79.9	90.4
		Asia	158	119	75.3	67.8	81.8
A/Victoria/210/2009 (H3N2)	D-QIV	US	589	414	70.3	66.4	74.0
		Europe	655	481	73.4	69.9	76.8
		Asia	557	392	70.4	66.4	74.1
	TIV-1	US	198	127	64.1	57.0	70.8
		Europe	219	145	66.2	59.5	72.4
		Asia	188	126	67.0	59.8	73.7
	TIV-2	US	183	117	63.9	56.5	70.9
		Europe	189	136	72.0	65.0	78.2
		Asia	158	118	74.7	67.2	81.3
B/Brisbane/60/2008 (Victoria)	D-QIV	US	589	317	53.8	49.7	57.9
		Europe	655	391	59.7	55.8	63.5
		Asia	557	338	60.7	56.5	64.8
	TIV-1	US	198	105	53.0	45.8	60.1
		Europe	219	119	54.3	47.5	61.1
		Asia	188	111	59.0	51.7	66.1
	TIV-2	US	183	86	47.0	39.6	54.5
		Europe	189	85	45.0	37.7	52.4
		Asia	158	81	51.3	43.2	59.3
B/Brisbane/3/2007(Yamagata)	D-QIV	US	589	335	56.9	52.8	60.9
		Europe	655	430	65.6	61.9	69.3
		Asia	557	347	62.3	58.1	66.3
	TIV-1	US	198	87	43.9	36.9	51.2
		Europe	219	106	48.4	41.6	55.2
		Asia	188	83	44.1	36.9	51.6
	TIV-2	US	183	109	59.6	52.1	66.7
		Europe	189	110	58.2	50.8	65.3

				SCR			
						95% CI	
Strain	Group	Sub-group	N	n	%	LL	UL
		Asia	158	94	59.5	51.4	67.2

US = Subjects from United States
Europe = Subjects from Germany, Romania and Spain
Asia = Subjects from Korea and Taiwan
Seroconversion defined as:
For initially seronegative subjects, antibody titer ≥ 40 1/DIL after vaccination
For initially seropositive subjects, antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer
N = Number of subjects with pre- and post-vaccination results available
n/% = Number/percentage of seroconverted subjects

Reviewer's comment

The seroconversion rates are similar in the three regions for the four strains, the bigger difference observed was the SCR between US and Europe for the A/Victoria/210/2009 (H3N2) strain and TIV-2 group (64% for US and 72% for Europe).

Table 30: Seroprotection rates (SPR) for HI antibodies against each strain at day 0 and day 21 by region (ATP cohort for immunogenicity)

Strain	Group	Sub-group	Timing	N	SPR			
					n	%	95% CI	
							LL	UL
A/California/7/2009 (H1N1)	D-QIV	US	PRE	589	206	35	31.1	39
			PI(D21)	593	559	94.3	92.1	96
		Europe	PRE	655	156	23.8	20.6	27.3
			PI(D21)	659	578	87.7	85	90.1
		Asia	PRE	557	152	27.3	23.6	31.2
			PI(D21)	557	514	92.3	89.7	94.4
	TIV-1	US	PRE	198	65	32.8	26.3	39.8
			PI(D21)	200	190	95	91	97.6
		Europe	PRE	219	46	21	15.8	27
			PI(D21)	220	195	88.6	83.7	92.5
		Asia	PRE	188	56	29.8	23.4	36.9
			PI(D21)	188	173	92	87.2	95.5
	TIV-2	US	PRE	183	60	32.8	26	40.1
			PI(D21)	183	175	95.6	91.6	40.1
		Europe	PRE	189	32	16.9	11.9	40.1
			PI(D21)	193	178	92.2	87.5	40.1
		Asia	PRE	158	47	29.7	22.7	40.1
			PI(D21)	158	142	89.9	84.1	40.1
A/Victoria/210/2009 (H3N2)	D-QIV	US	PRE	589	312	53	48.8	40.1
			PI(D21)	593	564	95.1	93.1	40.1
		Europe	PRE	655	340	51.9	48	40.1
			PI(D21)	659	639	97	95.4	40.1
		Asia	PRE	557	313	56.2	52	40.1
			PI(D21)	557	548	98.4	97	40.1
	TIV-1	US	PRE	198	115	58.1	50.9	40.1
			PI(D21)	200	190	95	91	40.1
		Europe	PRE	219	117	53.4	46.6	40.1
			PI(D21)	220	209	95	91.2	40.1
		Asia	PRE	188	121	64.4	57.1	40.1

Strain	Group	Sub-group	Timing	N	SPR			
					n	%	95% CI	
							LL	UL
			PI(D21)	188	184	97.9	94.6	40.1
	TIV-2	US	PRE	183	108	59	51.5	40.1
			PI(D21)	183	175	95.6	91.6	40.1
		Europe	PRE	189	96	50.8	43.4	40.1
			PI(D21)	193	187	96.9	93.4	40.1
		Asia	PRE	158	81	51.3	43.2	40.1
			PI(D21)	158	155	98.1	94.6	40.1
B/Brisbane/60/2008(Victoria)	D-QIV	US	PRE	589	517	87.8	84.9	40.1
			PI(D21)	593	591	99.7	98.8	40.1
		Europe	PRE	655	521	79.5	76.2	40.1
			PI(D21)	659	654	99.2	98.2	40.1
		Asia	PRE	557	385	69.1	65.1	40.1
			PI(D21)	557	543	97.5	95.8	40.1
	TIV-1	US	PRE	198	167	84.3	78.5	40.1
			PI(D21)	200	197	98.5	95.7	40.1
		Europe	PRE	219	179	81.7	76	40.1
			PI(D21)	220	217	98.6	96.1	40.1
		Asia	PRE	188	131	69.7	62.6	40.1
			PI(D21)	188	185	98.4	95.4	40.1
	TIV-2	US	PRE	183	158	86.3	80.5	40.1
			PI(D21)	183	181	98.9	96.1	40.1
		Europe	PRE	189	151	79.9	73.5	40.1
			PI(D21)	193	187	96.9	93.4	40.1
		Asia	PRE	158	103	65.2	57.2	40.1
			PI(D21)	158	145	91.8	86.3	40.1
B/Brisbane/3/2007(Yamagata)	D-QIV	US	PRE	589	520	88.3	85.4	40.1
			PI(D21)	593	591	99.7	98.8	40.1
		Europe	PRE	655	519	79.2	75.9	40.1
			PI(D21)	659	648	98.3	97	40.1
		Asia	PRE	557	455	81.7	78.2	40.1
			PI(D21)	557	553	99.3	98.2	40.1
	TIV-1	US	PRE	198	177	89.4	84.2	40.1
			PI(D21)	200	200	100	98.2	40.1
		Europe	PRE	219	173	79	73	40.1
			PI(D21)	220	212	96.4	93	40.1
		Asia	PRE	188	147	78.2	71.6	40.1
			PI(D21)	188	183	97.3	93.9	40.1
	TIV-2	US	PRE	183	166	90.7	85.5	40.1
			PI(D21)	183	183	100	98	40.1
		Europe	PRE	189	147	77.8	71.2	40.1
			PI(D21)	193	192	99.5	97.1	40.1
		Asia	PRE	158	128	81	74	40.1
			PI(D21)	158	157	99.4	96.5	40.1

US = Subjects from United States
Europe = Subjects from Germany, Romania and Spain
Asia = Subjects from Korea and Taiwan
N = Number of subjects with available results
n/% = Number/percentage of seroprotected subjects (HI titer ≥ 40 1/DIL)

PRE = visit 1 Day 0, PI(D21)= visit 2 Day 21

3.1.3.4.5 Immunogenicity Results by Race

The total vaccinated cohort is predominantly White/Caucasian and can mainly be divided into two categories based on race as White/Caucasian and non-White/Caucasian for analysis by race (refer to table 27 for full demographic characteristics).

Table 31 presents a summary of demographic characteristics by race (White/Caucasian vs. Non-White/Caucasian subjects) for the three treatment groups for the total vaccinated cohort.

Tables 32-34 presents Seropositivity rates and GMT (table 32), Seroconversion rates (table 33), and Seroprotection rates (table 34) for the HI antibodies against each of the four strains at day 0 and day 21 by race for the ATP cohort for immunogenicity.

Table 31: Summary of demographic characteristics by race (Total vaccinated cohort)

Character-istics	Parameters or Categories	D--IV				TIV-1				TIV-2				Total			
		White/ Caucasian N = 2078		Non- White/ Caucasian N = 958		White/ Caucasian N=699		Non- White/ Caucasian N = 311		White/ Caucasian N =414		Non- White/ Caucasian N = 196		White/ Caucasian N = 3191		Non- White/ Caucasian N = 1465	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age (years) at Vaccination Dose: 1	Mean	59.8	-	53.8	-	59.7	-	54.4	-	60.3	-	53.7	-	59.8	-	53.9	-
	SD	16.88	-	18.74	-	16.96	-	19.18	-	16.8	-	19.38	-	16.88	-	18.91	-
	Median	65	-	58	-	65	-	63	-	66	-	60	-	65	-	59	-
	Minimum	18	-	18	-	18	-	18	-	18	-	18	-	18	-	18	-
	Maximum	91	-	92	-	92	-	90	-	90	-	88	-	92	-	92	-
Gender	Female	1200	57.7	545	56.9	380	54.4	168	54	237	57.2	106	54.1	1817	56.9	819	55.9
	Male	878	42.3	413	43.1	319	45.6	143	46	177	42.8	90	45.9	1374	43.1	646	44.1
Ethnicity	American hispanic or	112	5.4	22	2.3	39	5.6	8	2.6	19	4.6	6	3.1	170	5.3	36	2.5
	Not American Hispanic or Latino	1966	94.6	936	97.7	660	94.4	303	97.4	395	95.4	190	96.9	3021	94.7	1429	97.5
Geographic Ancestry	African/Africa n American	0	0	106	11.1	0	0	26	8.4	0	0	21	10.7	0	0	153	10.4
	American Indian or Alaskan native	0	0	6	0.6	0	0	2	0.6	0	0	3	1.5	0	0	11	0.8

Character-istics	Parameters or Categories	D--IV				TIV-1				TIV-2				Total			
		White/ Caucasian N = 2078		Non- White/ Caucasian N = 958		White/ Caucasian N=699		Non- White/ Caucasian N = 311		White/ Caucasian N =414		Non- White/ Caucasian N = 196		White/ Caucasian N = 3191		Non- White/ Caucasian N = 1465	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
	Asian - Central/South Asian	0	0	5	0.5	0	0	2	0.6	0	0	1	0.5	0	0	8	0.5
	Asian - East Asian	0	0	799	83.4	0	0	267	85.9	0	0	160	81.6	0	0	1226	83.7
	Asian - Japanese heritage	0	0	0	0	0	0	0	0	0	0	1	0.5	0	0	1	0.1
	Asian - South East Asian	0	0	1	0.1	0	0	1	0.3	0	0	0	0	0	0	2	0.1
	Native Hawaiian or other Pacific Islander	0	0	2	0.2	0	0	0	0	0	0	0	0	0	0	2	0.1
	White Arabic/ North African	0	0	22	2.3	0	0	7	2.3	0	0	4	2	0	0	33	2.3
	White - Caucasian / European	2078	100	0	0	699	100	0	0	414	100	0	0	3191	100	0	0
	Other	0	0	17	1.8	0	0	6	1.9	0	0	6	3.1	0	0	29	2

Table 32: Seropositivity and GMTs for HI antibodies against each strain at day 0 and day 21 by race

Antibody	Group	Sub-group	Timing	N	≥ 10 1/DIL				GMT		
							95% CI			95% CI	
					n	%	LL	UL	value	LL	UL
A/CAL/7/09 (H1N1)	D-QIV	White/Caucasian	PRE	1143	645	56.4	53.5	59.3	15	14	16.1
			PI(D21)	1151	1094	95	93.6	96.2	199.8	183	218.2
		Non-White/ Caucasian	PRE	658	322	48.9	45.1	52.8	14.1	12.8	15.6
			PI(D21)	658	644	97.9	96.5	98.8	203.4	183.7	225.3
	TIV-1	White/Caucasian	PRE	392	233	59.4	54.4	64.3	15.8	13.8	18
			PI(D21)	395	380	96.2	93.8	97.9	220.8	189.5	257.2
		Non- White/ Caucasian	PRE	213	119	55.9	48.9	62.6	15.4	13	18.3
			PI(D21)	213	206	96.7	93.3	98.7	214.1	178.7	256.5
	TIV-2	White/Caucasian	PRE	340	191	56.2	50.7	61.5	13.8	12.1	15.7
			PI(D21)	344	332	96.5	94	98.2	214.9	183.6	251.6
		Non- White/ Caucasian	PRE	190	100	52.6	45.3	59.9	15.4	12.7	18.7
			PI(D21)	190	182	95.8	91.9	98.2	209.6	168.6	260.5
A/Victoria/210/09 (H3N2)	D-QIV	White/Caucasian	PRE	1143	908	79.4	77	81.7	33.3	30.7	36.2
			PI(D21)	1151	1128	98	97	98.7	296.4	274.6	319.8
		Non- White/ Caucasian	PRE	658	508	77.2	73.8	80.4	35.2	31.5	39.3
			PI(D21)	658	655	99.5	98.7	99.9	349.4	319.6	382.1

Antibody	Group	Sub-group	Timing	N	≥ 10 1/DIL				GMT		
							95% CI			95% CI	
					n	%	LL	UL	value	LL	UL
	TIV-1	White/Caucasian	PRE	392	312	79.6	75.3	83.5	36.1	31.3	41.6
			PI(D21)	395	385	97.5	95.4	98.8	274.2	239.7	313.8
		Non- White/ Caucasian	PRE	213	176	82.6	76.9	87.5	42.2	35.1	50.8
			PI(D21)	213	209	98.1	95.3	99.5	348.3	294.7	411.6
	TIV-2	White/Caucasian	PRE	340	269	79.1	74.4	83.3	35.6	30.4	41.6
			PI(D21)	344	338	98.3	96.2	99.4	316.9	274.9	365.4
		Non- White/ Caucasian	PRE	190	156	82.1	75.9	87.3	35.8	29.4	43.8
			PI(D21)	190	190	100	98.1	100	387.5	323	464.9
B/Bri/60/08 (Victoria)	D-QIV	White/Caucasian	PRE	1143	1017	89	87	90.7	89.1	82.3	96.4
			PI(D21)	1151	1146	99.6	99	99.9	451.5	428.2	476
		Non- White/ Caucasian	PRE	658	524	79.6	76.4	82.6	53.2	47.6	59.6
			PI(D21)	658	649	98.6	97.4	99.4	334.1	307.6	362.7
	TIV-1	White/Caucasian	PRE	392	345	88	84.4	91.1	89.5	77.8	103
			PI(D21)	395	391	99	97.4	99.7	440	398.4	486
		Non- White/ Caucasian	PRE	213	166	77.9	71.8	83.3	51.4	42	62.9
			PI(D21)	213	210	98.6	95.9	99.7	320.5	277.9	369.7
	TIV-2	White/Caucasian	PRE	340	300	88.2	84.3	91.5	88.5	76.3	102.6
			PI(D21)	344	337	98	95.9	99.2	313.9	282	349.5
		Non- White/ Caucasian	PRE	190	152	80	73.6	85.4	49.1	40	60.4
			PI(D21)	190	181	95.3	91.2	97.8	181.8	151.6	218
B/Bri/3/07 (Yamagata)	D-QIV	White/Caucasian	PRE	1143	983	86	83.9	88	106.3	97.1	116.3
			PI(D21)	1151	1139	99	98.2	99.5	610.5	574.2	649.2
		Non- White/ Caucasian	PRE	658	571	86.8	83.9	89.3	93.6	83.6	104.7
			PI(D21)	658	655	99.5	98.7	99.9	586.7	542.4	634.7
	TIV-1	White/Caucasian	PRE	392	340	86.7	83	89.9	109.8	94.4	127.8
			PI(D21)	395	388	98.2	96.4	99.3	407.5	361.9	458.9
		Non- White/Caucasian	PRE	213	185	86.9	81.6	91.1	86.2	70.3	105.7
			PI(D21)	213	209	98.1	95.3	99.5	350.7	298.9	411.5
	TIV-2	White/Caucasian	PRE	340	293	86.2	82	89.7	104.2	88.5	122.8
			PI(D21)	344	343	99.7	98.4	100	634.9	574.7	701.3
		Non- White/ Caucasian	PRE	190	164	86.3	80.6	90.9	92.2	74.6	114
			PI(D21)	190	189	99.5	97.1	100	498.5	425	584.6

Table 33: Seroconversion rate (SCR) for HI antibodies against each strain at day 21 by race

Strain	Group	Sub-group	N	SCR			
						95% CI	
				N	%	LL	UL
A/CAL/7/09 (H1N1)	D-QIV	White/Caucasian	1143	885	77.4	74.9	79.8
		Non-White/Caucasian	658	511	77.7	74.3	80.8
	TIV-1	White/Caucasian	392	302	77.0	72.6	81.1
		Non-White/Caucasian	213	165	77.5	71.3	82.9
	TIV-2	White/Caucasian	340	280	82.4	77.9	86.3
		Non-White/Caucasian	190	145	76.3	69.6	82.2
A/Victoria/210/09 (H3N2)	D-QIV	White/Caucasian	1143	809	70.8	68.0	73.4
		Non-White/Caucasian	658	478	72.6	69.1	76.0
	TIV-1	White/Caucasian	392	254	64.8	59.8	69.5
		Non-White/Caucasian	213	144	67.6	60.9	73.8
	TIV-2	White/Caucasian	340	232	68.2	63.0	73.2
		Non-White/Caucasian	190	139	73.2	66.3	79.3

Strain	Group	Sub-group	N	SCR			
						95% CI	
				N	%	LL	UL
B/Bri/60/08 (Victoria)	D-QIV	White/Caucasian	1143	636	55.6	52.7	58.5
		Non-White/Caucasian	658	410	62.3	58.5	66.0
	TIV-1	White/Caucasian	392	208	53.1	48.0	58.1
		Non-White/Caucasian	213	127	59.6	52.7	66.3
	TIV-2	White/Caucasian	340	158	46.5	41.1	51.9
		Non-White/Caucasian	190	94	49.5	42.2	56.8
B/Bri/3/07 (Yamagata)	D-QIV	White/Caucasian	1143	691	60.5	57.6	63.3
		Non-White/Caucasian	658	421	64.0	60.2	67.7
	TIV-1	White/Caucasian	392	174	44.4	39.4	49.5
		Non-White/Caucasian	213	102	47.9	41.0	54.8
	TIV-2	White/Caucasian	340	199	58.5	53.1	63.8
		Non-White/Caucasian	190	114	60.0	52.7	67.0

Table 36: Seroprotection rates for HI antibodies against each strain at day 0 and day 21 by race

					SPR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
A/CAL/7/09 (H1N1)	D-QIV	White/Caucasian	PRE	1143	331	29.0	26.3	31.7
			PI(D21)	1151	1040	90.4	88.5	92.0
		Non-White/Caucasian	PRE	658	183	27.8	24.4	31.4
			PI(D21)	658	611	92.9	90.6	94.7
	TIV-1	White/Caucasian	PRE	392	106	27.0	22.7	31.7
			PI(D21)	395	360	91.1	87.9	93.8
		Non-White/Caucasian	PRE	213	61	28.6	22.7	35.2
			PI(D21)	213	198	93.0	88.7	96.0
	TIV-2	White/Caucasian	PRE	340	78	22.9	18.6	27.8
			PI(D21)	344	322	93.6	90.5	95.9

					SPR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
		Non-White/Caucasian	PRE	190	61	32.1	25.5	39.2
			PI(D21)	190	173	91.1	86.1	94.7
A/Victoria/210/09 (H3N2)	D-QIV	White/Caucasian	PRE	1143	596	52.1	49.2	55.1
			PI(D21)	1151	1103	95.8	94.5	96.9
		Non-White/Caucasian	PRE	658	369	56.1	52.2	59.9
			PI(D21)	658	648	98.5	97.2	99.3
	TIV-1	White/Caucasian	PRE	392	223	56.9	51.8	61.8
			PI(D21)	395	377	95.4	92.9	97.3
		Non-White/Caucasian	PRE	213	130	61.0	54.1	67.6
			PI(D21)	213	206	96.7	93.3	98.7
	TIV-2	White/Caucasian	PRE	340	183	53.8	48.4	59.2
			PI(D21)	344	331	96.2	93.6	98.0
		Non-White/Caucasian	PRE	190	102	53.7	46.3	60.9
			PI(D21)	190	186	97.9	94.7	99.4
B/Bri/60/08 (Victoria)	D-QIV	White/Caucasian	PRE	1143	954	83.5	81.2	85.6
			PI(D21)	1151	1145	99.5	98.9	99.8
		Non-White/Caucasian	PRE	658	469	71.3	67.7	74.7
			PI(D21)	658	643	97.7	96.3	98.7
	TIV-1	White/Caucasian	PRE	392	327	83.4	79.4	87.0
			PI(D21)	395	390	98.7	97.1	99.6
		Non-White/Caucasian	PRE	213	150	70.4	63.8	76.5
			PI(D21)	213	209	98.1	95.3	99.5
	TIV-2	White/Caucasian	PRE	340	282	82.9	78.5	86.8
			PI(D21)	344	336	97.7	95.5	99.0
		Non-White/Caucasian	PRE	190	130	68.4	61.3	75.0
			PI(D21)	190	177	93.2	88.6	96.3
B/Bri/3/07 (Yamagata)	D-QIV	White/Caucasian	PRE	1143	949	83.0	80.7	85.2
			PI(D21)	1151	1138	98.9	98.1	99.4
		Non-White/Caucasian	PRE	658	545	82.8	79.7	85.6
			PI(D21)	658	654	99.4	98.5	99.8
	TIV-1	White/Caucasian	PRE	392	330	84.2	80.2	87.7
			PI(D21)	395	387	98.0	96.0	99.1
		Non-White/Caucasian	PRE	213	167	78.4	72.3	83.7
			PI(D21)	213	208	97.7	94.6	99.2
	TIV-2	White/Caucasian	PRE	340	283	83.2	78.8	87.0
			PI(D21)	344	343	99.7	98.4	100
		Non-White/Caucasian	PRE	190	158	83.2	77.1	88.2
			PI(D21)	190	189	99.5	97.1	100

3.1.3.5 Immunogenicity Conclusions

The pre-specified criteria for:

- Lot-to-lot consistencies in terms of GMT ratio were met for the three considered lots of D-QIV for the primary objective of D-QIV lot to lot consistency.
- Immunological non-inferiority of D-QIV for each of the four strains relative to TIV vaccines with respect to GMT ratio and SCR difference were met.

- Immunological superiority of D-QIV over the TIV for the B strain that is not included in the TIV vaccines with respect to GMT ratio and SCR difference were met.

Please refer section 3.1.3 for the details of immunological evaluations and results.

3.1.4 Evaluation of Safety and Results

3.1.4.1 Total Vaccinated Cohort Analysis

The analysis of safety was performed on the Total vaccinated cohort. The number and percentage of subjects who received vaccine dose are presented in table 37. Tabulations by gender and age strata are presented in tables 38 and 39 respectively.

Table 37: Number and percentage of subjects who received the study vaccine dose (Total vaccinated cohort)

D-QIV N = 3036		TIV-1 N = 1010		TIV-2 N = 610		Total N = 4656	
n	%	n	%	n	%	n	%
3036	100	1010	100	610	100	4656	100

N = number of subjects in each group or in total included in the considered cohort
n/% = number/percentage of subjects receiving the dose

Table 38: Number and percentage of subjects who received the study vaccine dose by gender (Total vaccinated cohort)

D-QIV				TIV-1				TIV-2				Total			
Male N = 1291		Female N = 1745		Male N = 462		Female N = 548		Male N = 267		Female N = 343		Male N = 2020		Female N = 2636	
n	%	n	%	n	%	n	%	N	%	n	%	n	%	n	%
1291	100	1745	100	462	100	548	100	267	100	343	100	2020	100	2636	100

N = number of subjects in each group or in total included in the considered cohort
n/% = number/percentage of subjects receiving the dose

Table 39: Number and percentage of subjects who received the study vaccine dose by age strata (18-64 and ≥ 65) (Total vaccinated cohort)

D-QIV				TIV-1				TIV-2				Total			
18-64y N = 1519		**≥ 65** N = 1517		18-64y N = 506		**≥ 65** N = 504		18-64y N = 301		**≥ 65** N = 309		18-64y N = 2326		**≥ 65** N = 2330	
n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
1519	100	1517	100	506	100	504	100	301	100	309	100	2326	100	2330	100

N = number of subjects in each group or in total included in the considered cohort
n/% = number/percentage of subjects receiving the dose

3.1.4.1.1 Overall Incidence of Adverse Events

The incidence and nature of solicited and unsolicited AEs reported during the 7-day (Days 0-6) post-vaccination period is presented in table 40 (any grade) and table 41 (grade 3).

Table 40: Incidence and nature of symptoms (solicited and unsolicited) reported during

the 7-day (Days 0-6) post-vaccination period (Total vaccinated cohort)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
D-QIV	3036	1504	49.5	47.7	51.3	3036	1048	34.5	32.8	36.2	3036	1123	37.0	35.3	38.7
TIV-1	1010	521	51.6	48.5	54.7	1010	366	36.2	33.3	39.3	1010	378	37.4	34.4	40.5
TIV-2	610	294	48.2	44.2	52.2	610	203	33.3	29.5	37.2	610	195	32.0	28.3	35.8

N= number of subjects with the administered dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

Table 41: Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period (Total vaccinated cohort)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
D-QIV	3036	79	2.6	2.1	3.2	3036	62	2.0	1.6	2.6	3036	25	0.8	0.5	1.2
TIV-1	1010	26	2.6	1.7	3.7	1010	18	1.8	1.1	2.8	1010	12	1.2	0.6	2.1
TIV-2	610	15	2.5	1.4	4.0	610	12	2.0	1.0	3.4	610	3	0.5	0.1	1.4

N= number of subjects with the administered dose
0n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

Reviewer's comment:
The percentages of subjects reporting any local symptoms, any general symptoms, or any symptoms (local or general, or an unsolicited adverse event) appeared to be similar in all three groups. There did not appear to be any clinically relevant differences between the percentages of subjects reporting the AEs in the three groups.

The applicant reported incidence and nature of causally related solicited and unsolicited AEs reported during the 7-Day (Days 0-6) post-vaccination period. (Please see Supplement 59 for any grade and Supplement 60 for grade 3 on page 244 of the submitted study report).

3.1.4.1.2 Solicited local adverse events

The percentage of subjects reporting solicited local AEs (any grade/by grade) during the 7-day post-vaccination period is presented in table 42.

Table 42: Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total vaccinated cohort)

		D-QIV					TIV-1					TIV					Total				
					95 % CI					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Pain	All	3015	1096	36.4	34.6	38.1	1003	369	36.8	33.8	39.9	607	190	31.3	27.6	35.2	4625	1655	35.8	34.4	37.2
	Grade 1	3015	1073	35.6	33.9	37.3	1003	362	36.1	33.1	39.2	607	186	30.6	27.0	34.5	4625	1621	35.0	33.7	36.4

		D-QIV					TIV-1					TIV					Total				
					95 % CI					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
	Grade 2	3015	142	4.7	4.0	5.5	1003	45	4.5	3.3	6.0	607	29	4.8	3.2	6.8	4625	216	4.7	4.1	5.3
	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	4625	39	0.8	0.6	1.2
Redness (mm)	All	3015	58	1.9	1.5	2.5	1003	17	1.7	1.0	2.7	607	12	2.0	1.0	3.4	4625	87	1.9	1.5	2.3
	[20.1 - 50.1[	3015	52	1.7	1.3	2.3	1003	13	1.3	0.7	2.2	607	11	1.8	0.9	3.2	4625	76	1.6	1.3	2.1
	[50.1 - 100.1[	3015	11	0.4	0.2	0.7	1003	5	0.5	0.2	1.2	607	1	0.2	0.0	0.9	4625	17	0.4	0.2	0.6
	[100.1 - ...	3015	1	0.0	0.0	0.2	1003	0	0.0	0.0	0.4	607	0	0.0	0.0	0.6	4625	1	0.0	0.0	0.1
Swelling (mm)	All	3015	62	2.1	1.6	2.6	1003	21	2.1	1.3	3.2	607	8	1.3	0.6	2.6	4625	91	2.0	1.6	2.4
	[20.1 - 50.1[	3015	57	1.9	1.4	2.4	1003	17	1.7	1.0	2.7	607	8	1.3	0.6	2.6	4625	82	1.8	1.4	2.2
	[50.1 - 100.1[	3015	16	0.5	0.3	0.9	1003	7	0.7	0.3	1.4	607	2	0.3	0.0	1.2	4625	25	0.5	0.4	0.8
	[100.1 - ...	3015	0	0.0	0.0	0.1	1003	0	0.0	0.0	0.4	607	0	0.0	0.0	0.6	4625	0	0.0	0.0	0.1

N= number of subjects with the documented dose
n/%= number/percentage of subjects reporting the symptom at least once
Total : n/%= number/percentage of subjects with at least one local symptom

Injection site pain was the most frequently reported local AE across treatment groups (reported by 36.4%, 36.8%, and 31.3% of subjects in the D-QIV TIV-1 and TIV-2 groups respectively). Grade 3 local pain was reported by 0.8%, 1.2% and 0.5% of subjects in the D-QIV, TIV-1, and TIV-2 groups, respectively.

3.1.4.1.3 Solicited general adverse events

Fatigue, headache and muscle aches were the most frequently reported general AEs across the treatment groups. Fatigue was respectively reported by 15.8%, 18.4% and 14.8% of subjects in the D-QIV, TIV-1 groups TIV-2 groups. Headache was respectively reported by 15.9%, 16.4%, and 13.2% of subjects in the D-QIV, TIV-1 and TIV-2 groups. Muscle ache was reported by 16.4%, 19.4% and 16.1% of subjects in the D-QIV TIV-1 TIV-2 groups, respectively.

Grade 3 solicited general AEs were reported by less than 1% subjects in all treatment groups.

Fever was reported by 1.6%, 1.2% and 1.5% of subjects in the D-QIV, TIV-1, and TIV-2 groups respectively. Fever related to vaccination was reported by 1.0%, 0.5% and 1.0% of subjects in the D-QIV, TIV-1and TIV-2 groups, respectively.

3.1.4.1.4 Unsolicited adverse events

A global summary of unsolicited AE reported within 21-day (Day 0-20) post-vaccination period is presented in table 43 and table 44 for grade 3.

Table 43: Global summary of unsolicited adverse events reported within the 21-day (Days 0-20) post-vaccination period (Total vaccinated cohort)

	Group			
	D-QIV	TIV-1	TIV-2	Total

	Group			
	D-QIV	TIV-1	TIV-2	Total
Number of subjects with at least one unsolicited symptom reported	379	138	92	609
Number of doses followed by at least one unsolicited symptom	379	138	92	609
Number of unsolicited symptoms classified by MedDRA Preferred Term*	558	195	125	878
Number of unsolicited symptoms reported	574	197	126	897

* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once

Overall, 897 unsolicited AEs were reported by 609 subjects (379 subjects [12.5%] in the D-QIV group, 138 subjects [13.7%] in the TIV-1 group and 92 subjects [15.1%] in the TIV-2 group) during the 21-day follow-up period. Nasopharyngitis and cough are the most frequent reported unsolicited AE during this period, reported by 1.4 to 1.7% of the subjects across the different treatment groups.

Table 44: Global summary of grade 3 unsolicited adverse events reported within the 21-day (Days 0-20) post-vaccination period (Total vaccinated cohort)

	Group			
	D-QIV	TIV-1	TIV-2	Total
Number of subjects with at least one unsolicited symptom reported	39	7	2	48
Number of doses followed by at least one unsolicited symptom	39	7	2	48
Number of unsolicited symptoms classified by MedDRA Preferred Term*	52	8	2	62
Number of unsolicited symptoms reported	53	8	2	63

* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once

A global summary of unsolicited AE reported with causal relationship to vaccination within 21-day (Day 0-20) post-vaccination period is presented in table 45 and grade 3 with causal relationship in Table 46, and a global summary of unsolicited AE reported with medically attended visits within 21 days (days 0-20) post vaccination period is presented in table 47.

Table 45: Global summary of unsolicited adverse events reported with causal relationship to vaccination, within the 21-day (Days 0-20) post- vaccination period (Total vaccinated cohort)

	Group			
	D-QIV	TIV-1	TIV-2	Total
Number of subjects with at least one unsolicited symptom reported	64	26	14	104
Number of doses followed by at least one unsolicited symptom	64	26	14	104
Number of unsolicited symptoms classified by MedDRA Preferred Term*	89	38	16	143
Number of unsolicited symptoms reported	92	38	16	146

* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once

Table 46: Global summary of grade 3 unsolicited adverse events reported with causal relationship to vaccination, within the 21-day (Days 0-20) post-vaccination

period (Total vaccinated cohort)

	Group			
	D-QIV	TIV-1	TIV-2	Total
Number of subjects with at least one unsolicited symptom reported	4	0	0	4
Number of doses followed by at least one unsolicited symptom	4	0	0	4
Number of unsolicited symptoms classified by MedDRA Preferred Term*	7	0	0	7
Number of unsolicited symptoms reported	8	0	0	8

* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once

Table 47: Global summary of unsolicited adverse events reported with medically attended visit, within the 21-day (Days 0-20) post- vaccination period (TVC)

	Group			
	D-QIV	TIV-1	TIV-2	Total
Number of subjects with at least one unsolicited symptom reported	193	60	47	300
Number of doses followed by at least one unsolicited symptom	193	60	47	300
Number of unsolicited symptoms classified by MedDRA Preferred Term*	250	75	63	388
Number of unsolicited symptoms reported	252	75	63	390

* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted.

During the 21-day post-vaccination period, 193 subjects (6.4%) in the D-QIV group, 60 subjects (5.9%) in the TIV-1 group and 47 subjects (7.7%) in the TIV-2 group had at least one unsolicited adverse events with medically attended visit.

Global summary of unsolicited AE with medically attended visit reported during the entire study period is presented in table 48.

Table 48: Global summary of unsolicited adverse events reported with medically attended visit, during the entire study period (TVC)

	Group			
	D-QIV	TIV-1	TIV-2	Total
Number of subjects with at least one unsolicited symptom reported	688	216	52**	956
Number of doses followed by at least one unsolicited symptom	688	216	52	956
Number of unsolicited symptoms classified by MedDRA Preferred Term*	1151	379	69	1599
Number of unsolicited symptoms reported	1183	391	69	1643

* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once

**In the TIV-2 group: 4 subjects reported an unsolicited AE with medically attended visit between Day 21 and Day 28 (allowed interval for the Day 21 visit) and 1 subject had by error a study contact after the last visit during which he reported an AE with medically attended visit with start date after Day 20. Note that a sixth subject had an unsolicited AE within 21 days post-vaccination and another one between Day 21 and Day 28. In this table, this subject is included once.

During the entire study period, 688 subjects (22.7%) in the D-QIV group and 216 subjects (21.4%) in the TIV-1 group had unsolicited adverse events with medically attended visit. TIV-2 group was followed only up to 21 day post-vaccination period, therefore the entire study period for the TIV-2 was approximately 21 days.

3.1.4.1.5 Serious Adverse Events (SAEs)

Fatal events

During the entire study period, fatal SAEs were reported for 12 subjects (9 in the D-QIV group and 3 in the TIV-1 group): all subjects were >65 years of age. None of these SAEs was assessed as causally related to vaccination.

- Five subjects died from cardiac disorders:
  - An 85-year-old female subject (D-QIV group) with angina pectoris and atrial fibrillation developed myocardial infarction and died of congestive heart failure 4 months post-vaccination.
  - A 72-year-old female subject (D-QIV group) with hypertriglyceridemia died of myocardial infarction 35 days post-vaccination.
  - An 86-year-old male subject (TIV-1 group) with hypertension, ischemic heart disease and chronic bronchitis experienced myocardial infarction and died of cardiac arrest 75 days post-vaccination.
  - A 69-year-old male subject (TIV-1 group) with heart failure, hypertension and diabetes mellitus died of cardiorespiratory arrest 97 days post-vaccination.
  - A 69-year-old male smoker (TIV-1 group) with ischemic cardiomyopathy, unstable angina and diabetes mellitus died of an unspecified cardiac disorder 15 days post-vaccinations.
- One subject died from neoplasms benign, malignant and unspecified (incl cysts and polyps)
  - A 71-year-old female subject (D-QIV group) with a 40-year history of smoking about one pack a day developed pneumonia 8 days post-vaccination, followed by myocardial infarction approximately 5 weeks later. She was diagnosed with small cell lung cancer 51 days post-vaccination and died 19 days later.
- One subject died from gastrointeinal disorders
  - An 81-year-old female subject (D-QIV group) experienced intestinal infarction 86 days post-vaccination. The next day, she developed acute cardiac and respiratory failure, and died of intestinal infarction.
- Two subjects died from general disorders and administration site conditions:
  - An 85-year-old male subject (D-QIV group) experienced sudden death 86 days post-vaccination.
  - An 84-year-old female subject (D-QIV group), with arrhythmia, developed erysipelas 60 days post-vaccination and experienced sudden death 2 days later.
- Two subjects died from nervous system disorders:
  - A 68-year-old female subject (D-QIV group), with liver cirrhosis, developed hepatic coma 95 days post-vaccination and died of the event approximately 1.5 months later.
  - A 73-year-old male subject (D-QIV group), with hypertension and left ventricular hypertrophy, experienced a stroke 6 months post-vaccination and died of the event within approximately 7 hours.
- One subject died from respiratory, thoracic and mediastinal disorders:
  - A 71-year-old male subject (D-QIV group), with COPD and pulmonary hypertension, developed an exacerbation of pulmonary hypertension 5 months post-vaccination followed by aspiration pneumonia approximately 3 weeks later. Although exacerbation of pulmonary hypertension was considered fatal, the subject was reported to have died of an unknown cause 6 weeks after the event onset despite extensive treatment.

Non-fatal SAEs

Table 49 presents global summaries of serious adverse events reported within the 21-day post-vaccination period and global summary of serious adverse events reported for the entire study period is presented in table 50.

Table 49: Global summary of serious adverse events reported within the 21-day (Days 0-20) post-vaccination period (Total vaccinated cohort)

	Group			
	D-QIV	TIV-1	TIV-2	Total
Number of subjects with at least one unsolicited symptom reported	16	6	1	23
Number of doses followed by at least one unsolicited symptom	16	6	1	23
Number of unsolicited symptoms classified by MedDRA Preferred Term*	18	6	1	25
Number of unsolicited symptoms reported	18	6	1	25

* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once

Within the 21-day period, 16 subjects (0.5%) in the D-QIV group, 6 subjects (0.6%) in the TIV-1 group and 1 subject (0.2%) in the TIV-2 group reported at least one SAE.

Table 50: Global summary of serious adverse events reported during entire study period (Total vaccinated cohort)

	Group			
	D-QIV	TIV-1	TIV-2	Total
Number of subjects with at least one unsolicited symptom reported	70	26	1	97
Number of doses followed by at least one unsolicited symptom	70	26	1	97
Number of unsolicited symptoms classified by MedDRA Preferred Term*	98	27	1	126
Number of unsolicited symptoms reported	99	27	1	127

* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once

During the entire study period, 70 subjects (2.3%) in the D-QIV group and 26 subjects (2.6%) in the TIV-1 group reported at least one SAE. TIV-2 group was followed only up to 21 day post-vaccination period; therefore, the entire study period for the TIV-2 was approximately 21 days.

None of the SAEs reported was assessed as related to the vaccine by the investigators.

3.1.4.2 Sub group Analysis of Safety

3.1.4.2.1 Overall Incidence of Adverse Events

Analysis by Age

The overall incidence and nature of solicited and unsolicited AEs, by age strata 18-64/65+, reported during the 7-day (Days 0-6) post-vaccination period is presented in table 51 below for any grade and table 52 for grade 3.

Table 51: Incidence and nature of symptoms (solicited and unsolicited) reported during

the 7-day (Days 0-6) post-vaccination period by age.

		Any symptom					General symptoms					Local symptoms				
	Sub-group				95% CI					95% CI					95% CI	
Group	(Age in years)	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
D-QIV	18-64	1519	973	64.1	61.6	66.5	1519	674	44.4	41.9	46.9	1519	780	51.3	48.8	53.9
	≥65	1517	531	35.0	32.6	37.5	1517	374	24.7	22.5	26.9	1517	343	22.6	20.5	24.8
TIV-1	18-64	506	329	65.0	60.7	69.2	506	232	45.8	41.4	50.3	506	263	52.0	47.5	56.4
	≥65y	504	192	38.1	33.8	42.5	504	134	26.6	22.8	30.7	504	115	22.8	19.2	26.7
TIV-2	18-64	301	177	58.8	53.0	64.4	301	115	38.2	32.7	44.0	301	141	46.8	41.1	52.7
	≥65	309	117	37.9	32.4	43.5	309	88	28.5	23.5	33.9	309	54	17.5	13.4	22.2

N= number of subjects with the administered dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

Table 52: Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period by age.

		Any symptom					General symptoms					Local symptoms				
	Sub-group				95% CI					95% CI					95% CI	
Group	(Age in years)	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
D-QIV	18-64	1519	52	3.4	2.6	4.5	1519	37	2.4	1.7	3.3	1519	21	1.4	0.9	2.1
	≥65	1517	27	1.8	1.2	2.6	1517	25	1.6	1.1	2.4	1517	4	0.3	0.1	0.7
TIV-1	18-64	506	18	3.6	2.1	5.6	506	12	2.4	1.2	4.1	506	9	1.8	0.8	3.3
	≥65y	504	8	1.6	0.7	3.1	504	6	1.2	0.4	2.6	504	3	0.6	0.1	1.7
TIV-2	18-64	301	9	3.0	1.4	5.6	301	6	2.0	0.7	4.3	301	3	1.0	0.2	2.9
	≥65	309	6	1.9	0.7	4.2	309	6	1.9	0.7	4.2	309	0	0.0	0.0	1.2

N= number of subjects with the administered dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

The overall incidence and nature of causally related solicited and unsolicited AEs reported during the 7-Day (Days 0-6) post-vaccination period is presented in table 53 for any grade and in table 54 for grade 3.

Table 53: Incidence and nature of symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 7-day (Days 0-6) post-vaccination period by age.

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
D-QIV	18-64	1519	891	58.7	56.1	61.1	1519	471	31.0	28.7	33.4	1519	779	51.3	48.7	53.8
	≥65	1517	432	28.5	26.2	30.8	1517	211	13.9	12.2	15.8	1517	342	22.5	20.5	24.7
TIV-1	18-64	506	302	59.7	55.3	64.0	506	166	32.8	28.7	37.1	506	263	52.0	47.5	56.4
	≥65y	504	155	30.8	26.7	35.0	504	71	14.1	11.2	17.4	504	115	22.8	19.2	26.7
TIV-2	18-64	301	162	53.8	48.0	59.6	301	77	25.6	20.7	30.9	301	141	46.8	41.1	52.7
	≥65	309	83	26.9	22.0	32.2	309	45	14.6	10.8	19.0	309	54	17.5	13.4	22.2

N= number of subjects with the administered dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

Table 54: Incidence and nature of grade 3 symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 7-day (Days 0-6) post-vaccination period by age.

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
D-QIV	18-64y	1519	38	2.5	1.8	3.4	1519	22	1.4	0.9	2.2	1519	21	1.4	0.9	2.1
	65y+	1517	12	0.8	0.4	1.4	1517	10	0.7	0.3	1.2	1517	4	0.3	0.1	0.7
TIV-1	18-64y	506	16	3.2	1.8	5.1	506	10	2.0	1.0	3.6	506	9	1.8	0.8	3.3
	65y+	504	6	1.2	0.4	2.6	504	4	0.8	0.2	2.0	504	3	0.6	0.1	1.7
TIV-2	18-64y	301	8	2.7	1.2	5.2	301	5	1.7	0.5	3.8	301	3	1.0	0.2	2.9
	65y+	309	5	1.6	0.5	3.7	309	5	1.6	0.5	3.7	309	0	0.0	0.0	1.2

N= number of subjects with the administered dose

n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

Analysis by Gender

The overall incidence and nature of solicited and unsolicited AEs, by gender, reported during the 7-day (Days 0-6) post-vaccination period is presented in table 55 for any grade and table 56 for grade 3.

Table 55: Incidence and nature of symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period by gender.

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
D-QIV	Male	1291	535	41.4	38.7	44.2	1291	365	28.3	25.8	30.8	1291	384	29.7	27.3	32.3
	Female	1745	969	55.5	53.2	57.9	1745	683	39.1	36.8	41.5	1745	739	42.3	40.0	44.7
TIV-1	Male	462	213	46.1	41.5	50.8	462	150	32.5	28.2	36.9	462	144	31.2	27.0	35.6
	Female	548	308	56.2	51.9	60.4	548	216	39.4	35.3	43.6	548	234	42.7	38.5	47.0
TIV-2	Male	267	127	47.6	41.4	53.7	267	96	36.0	30.2	42.0	267	78	29.2	23.8	35.1
	Female	343	167	48.7	43.3	54.1	343	107	31.2	26.3	36.4	343	117	34.1	29.1	39.4

N= number of subjects with the administered dose

n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

Table 56: Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period by gender.

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
D-QIV	Male	1291	23	1.8	1.1	2.7	1291	21	1.6	1.0	2.5	1291	2	0.2	0.0	0.6
	Female	1745	56	3.2	2.4	4.1	1745	41	2.3	1.7	3.2	1745	23	1.3	0.8	2.0
TIV-1	Male	462	13	2.8	1.5	4.8	462	7	1.5	0.6	3.1	462	9	1.9	0.9	3.7
	Female	548	13	2.4	1.3	4.0	548	11	2.0	1.0	3.6	548	3	0.5	0.1	1.6
TIV-2	Male	267	8	3.0	1.3	5.8	267	6	2.2	0.8	4.8	267	2	0.7	0.1	2.7
	Female	343	7	2.0	0.8	4.2	343	6	1.7	0.6	3.8	343	1	0.3	0.0	1.6

N= number of subjects with the administered dose

n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

The overall incidence and nature of causally related solicited and unsolicited AEs reported during the 7-Day (Days 0-6) post-vaccination period is presented in table 57 for any grade and table 58 for grade 3.

Table 57: Incidence and nature of symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 7-day (Days 0-6) post-

vaccination period by gender

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
D-QIV	Male	1291	462	35.8	33.2	38.5	1291	240	18.6	16.5	20.8	1291	383	29.7	27.2	32.2
	Female	1745	861	49.3	47.0	51.7	1745	442	25.3	23.3	27.4	1745	738	42.3	40.0	44.7
TIV-1	Male	462	181	39.2	34.7	43.8	462	87	18.8	15.4	22.7	462	144	31.2	27.0	35.6
	Female	548	276	50.4	46.1	54.6	548	150	27.4	23.7	31.3	548	234	42.7	38.5	47.0
TIV-2	Male	267	106	39.7	33.8	45.8	267	61	22.8	17.9	28.4	267	78	29.2	23.8	35.1
	Female	343	139	40.5	35.3	45.9	343	61	17.8	13.9	22.2	343	117	34.1	29.1	39.4

N= number of subjects with the administered dose

n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

Table 58: Incidence and nature of grade 3 symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 7-day (Days 0-6) post-vaccination period by gender.

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
D-QIV	Male	1291	9	0.7	0.3	1.3	1291	7	0.5	0.2	1.1	1291	2	0.2	0.0	0.6
	Female	1745	41	2.3	1.7	3.2	1745	25	1.4	0.9	2.1	1745	23	1.3	0.8	2.0
TIV-1	Male	462	11	2.4	1.2	4.2	462	5	1.1	0.4	2.5	462	9	1.9	0.9	3.7
	Female	548	11	2.0	1.0	3.6	548	9	1.6	0.8	3.1	548	3	0.5	0.1	1.6
TIV-2	Male	267	8	3.0	1.3	5.8	267	6	2.2	0.8	4.8	267	2	0.7	0.1	2.7
	Female	343	5	1.5	0.5	3.4	343	4	1.2	0.3	3.0	343	1	0.3	0.0	1.6

N= number of subjects with the administered dose

n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

Analysis by Race

The overall incidence and nature of solicited and unsolicited AEs, by race, reported during the 7-day (Days 0-6) post-vaccination period is presented in table 59 for any grade and table 60 for grade 3.

Table 59: Incidence and nature of symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period by race (TVC).

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
D-QIV	White/Caucasian	2078	1015	48.8	46.7	51.0	2078	684	32.9	30.9	35.0	2078	755	36.3	34.3	38.4
	Non-White/Caucasian	958	489	51.0	47.8	54.3	958	364	38.0	34.9	41.2	958	368	38.4	35.3	41.6
TIV-1	White/Caucasian	699	349	49.9	46.2	53.7	699	244	34.9	31.4	38.6	699	253	36.2	32.6	39.9
	Non-White/Caucasian	311	172	55.3	49.6	60.9	311	122	39.2	33.8	44.9	311	125	40.2	34.7	45.9
TIV-2	White/Caucasian	414	197	47.6	42.7	52.5	414	128	30.9	26.5	35.6	414	131	31.6	27.2	36.4
	Non-White/Caucasian	196	97	49.5	42.3	56.7	196	75	38.3	31.4	45.5	196	64	32.7	26.1	39.7

N= number of subjects with the administered dose

n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

Table 60: Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period by race (TVC).

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
D-QIV	White/Caucasian	2078	66	3.2	2.5	4.0	2078	51	2.5	1.8	3.2	2078	22	1.1	0.7	1.6

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
	Non-White/Caucasian	958	13	1.4	0.7	2.3	958	11	1.1	0.6	2.0	958	3	0.3	0.1	0.9
TIV-1	White/Caucasian	699	21	3.0	1.9	4.6	699	14	2.0	1.1	3.3	699	10	1.4	0.7	2.6
	Non-White/Caucasian	311	5	1.6	0.5	3.7	311	4	1.3	0.4	3.3	311	2	0.6	0.1	2.3
TIV-2	White/Caucasian	414	9	2.2	1.0	4.1	414	6	1.4	0.5	3.1	414	3	0.7	0.1	2.1
	Non-White/Caucasian	196	6	3.1	1.1	6.5	196	6	3.1	1.1	6.5	196	0	0.0	0.0	1.9

N= number of subjects with the administered dose

n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

The overall incidence and nature of symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 7-Day (Days 0-6) post-vaccination period by race is presented in table 61 for any grade and table 62 for grade 3.

Table 61: Incidence and nature of symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 7-day (Days 0-6) post-vaccination period by race (TVC).

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
D-QIV	White/Caucasian	2078	883	42.5	40.4	44.7	2078	422	20.3	18.6	22.1	2078	754	36.3	34.2	38.4
	Non-White/Caucasian	958	440	45.9	42.7	49.1	958	260	27.1	24.3	30.1	958	367	38.3	35.2	41.5
TIV-1	White/Caucasian	699	304	43.5	39.8	47.3	699	149	21.3	18.3	24.5	699	253	36.2	32.6	39.9
	Non-White/Caucasian	311	153	49.2	43.5	54.9	311	88	28.3	23.4	33.7	311	125	40.2	34.7	45.9
TIV-2	White/Caucasian	414	163	39.4	34.6	44.3	414	72	17.4	13.9	21.4	414	131	31.6	27.2	36.4
	Non-White/Caucasian	196	82	41.8	34.8	49.1	196	50	25.5	19.6	32.2	196	64	32.7	26.1	39.7

N= number of subjects with the administered dose

n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

Table 62: Incidence and nature of grade 3 symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 7-day (Days 0-6) post-vaccination period by race (TVC).

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
D-QIV	White/Caucasian	2078	42	2.0	1.5	2.7	2078	26	1.3	0.8	1.8	2078	22	1.1	0.7	1.6
	Non-White/Caucasian	958	8	0.8	0.4	1.6	958	6	0.6	0.2	1.4	958	3	0.3	0.1	0.9
TIV-1	White/Caucasian	699	18	2.6	1.5	4.0	699	11	1.6	0.8	2.8	699	10	1.4	0.7	2.6
	Non-White/Caucasian	311	4	1.3	0.4	3.3	311	3	1.0	0.2	2.8	311	2	0.6	0.1	2.3
TIV-2	White/Caucasian	414	8	1.9	0.8	3.8	414	5	1.2	0.4	2.8	414	3	0.7	0.1	2.1
	Non-White/Caucasian	196	5	2.6	0.8	5.9	196	5	2.6	0.8	5.9	196	0	0.0	0.0	1.9

N= number of subjects with the administered dose

n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

Analysis by Region

The overall incidence and nature of symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period by region is presented in table 63 for any grade and table 64 for grade 3.

Table 63: Incidence and nature of symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period by region (TVC).

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
D-QIV	US	946	516	54.5	51.3	57.8	946	363	38.4	35.3	41.6	946	376	39.7	36.6	42.9
	Europe	1288	590	45.8	43.1	48.6	1288	385	29.9	27.4	32.5	1288	448	34.8	32.2	37.5
	Asia	802	398	49.6	46.1	53.1	802	300	37.4	34.0	40.9	802	299	37.3	33.9	40.7
TIV-1	US	316	181	57.3	51.6	62.8	316	130	41.1	35.7	46.8	316	134	42.4	36.9	48.1
	Europe	426	193	45.3	40.5	50.2	426	132	31.0	26.6	35.6	426	138	32.4	28.0	37.1
	Asia	268	147	54.9	48.7	60.9	268	104	38.8	32.9	44.9	268	106	39.6	33.7	45.7
TIV-2	US	189	102	54.0	46.6	61.2	189	79	41.8	34.7	49.2	189	64	33.9	27.2	41.1
	Europe	259	120	46.3	40.1	52.6	259	70	27.0	21.7	32.9	259	86	33.2	27.5	39.3
	Asia	162	72	44.4	36.6	52.4	162	54	33.3	26.1	41.2	162	45	27.8	21.0	35.3

US = Subjects from United States
Europe = Subjects from Germany, Romania and Spain
Asia = Subjects from Korea and Taiwan
N= number of subjects with the administered dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

Table 64: Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period by region (TVC).

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
D-QIV	US	946	34	3.6	2.5	5.0	946	27	2.9	1.9	4.1	946	12	1.3	0.7	2.2
	Europe	1288	38	3.0	2.1	4.0	1288	29	2.3	1.5	3.2	1288	12	0.9	0.5	1.6
	Asia	802	7	0.9	0.4	1.8	802	6	0.7	0.3	1.6	802	1	0.1	0.0	0.7
TIV-1	US	316	13	4.1	2.2	6.9	316	10	3.2	1.5	5.7	316	6	1.9	0.7	4.1
	Europe	426	11	2.6	1.3	4.6	426	6	1.4	0.5	3.0	426	5	1.2	0.4	2.7
	Asia	268	2	0.7	0.1	2.7	268	2	0.7	0.1	2.7	268	1	0.4	0.0	2.1
TIV-2	US	189	5	2.6	0.9	6.1	189	5	2.6	0.9	6.1	189	0	0.0	0.0	1.9
	Europe	259	7	2.7	1.1	5.5	259	4	1.5	0.4	3.9	259	3	1.2	0.2	3.3
	Asia	162	3	1.9	0.4	5.3	162	3	1.9	0.4	5.3	162	0	0.0	0.0	2.3

US = Subjects from United States
Europe = Subjects from Germany, Romania and Spain
Asia = Subjects from Korea and Taiwan
N= number of subjects with the administered dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

The overall incidence and nature of symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 7-Day (Days 0-6) post-vaccination period by region is presented in table 65 for any grade and table 66 for grade 3.

Table 65: Incidence and nature of symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 7-day (Days 0-6) post-

vaccination period by region (TVC)..

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
D-QIV	US	946	467	49.4	46.1	52.6	946	269	28.4	25.6	31.4	946	374	39.5	36.4	42.7
	Europe	1288	496	38.5	35.8	41.2	1288	194	15.1	13.2	17.1	1288	448	34.8	32.2	37.5
	Asia	802	360	44.9	41.4	48.4	802	219	27.3	24.2	30.5	802	299	37.3	33.9	40.7
TIV-1	US	316	171	54.1	48.4	59.7	316	107	33.9	28.7	39.4	316	134	42.4	36.9	48.1
	Europe	426	156	36.6	32.0	41.4	426	57	13.4	10.3	17.0	426	138	32.4	28.0	37.1
	Asia	268	130	48.5	42.4	54.7	268	73	27.2	22.0	33.0	268	106	39.6	33.7	45.7
TIV-2	US	189	90	47.6	40.3	55.0	189	57	30.2	23.7	37.2	189	64	33.9	27.2	41.1
	Europe	259	96	37.1	31.2	43.3	259	31	12.0	8.3	16.6	259	86	33.2	27.5	39.3
	Asia	162	59	36.4	29.0	44.3	162	34	21.0	15.0	28.1	162	45	27.8	21.0	35.3

US = Subjects from United States
Europe = Subjects from Germany, Romania and Spain
Asia = Subjects from Korea and Taiwan
N= number of subjects with the administered dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

Table 66: Incidence and nature of grade 3 symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 7-day (Days 0-6) post-vaccination period by region.

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
D-QIV	US	946	22	2.3	1.5	3.5	946	14	1.5	0.8	2.5	946	12	1.3	0.7	2.2
	Europe	1288	24	1.9	1.2	2.8	1288	15	1.2	0.7	1.9	1288	12	0.9	0.5	1.6
	Asia	802	4	0.5	0.1	1.3	802	3	0.4	0.1	1.1	802	1	0.1	0.0	0.7
TIV-1	US	316	13	4.1	2.2	6.9	316	10	3.2	1.5	5.7	316	6	1.9	0.7	4.1
	Europe	426	8	1.9	0.8	3.7	426	3	0.7	0.1	2.0	426	5	1.2	0.4	2.7
	Asia	268	1	0.4	0.0	2.1	268	1	0.4	0.0	2.1	268	1	0.4	0.0	2.1
TIV-2	US	189	5	2.6	0.9	6.1	189	5	2.6	0.9	6.1	189	0	0.0	0.0	1.9
	Europe	259	6	2.3	0.9	5.0	259	3	1.2	0.2	3.3	259	3	1.2	0.2	3.3
	Asia	162	2	1.2	0.1	4.4	162	2	1.2	0.1	4.4	162	0	0.0	0.0	2.3

US = Subjects from United States
Europe = Subjects from Germany, Romania and Spain
Asia = Subjects from Korea and Taiwan
N= number of subjects with the administered dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

3.1.4.2.2 Serious Adverse Events

Analysis by Age

A global summary of serious adverse events reported within the 21-day post-vaccination period stratified by age is presented in table 67 and a global summary of serious adverse events reported during the entire study period stratified by age is presented in table 68.

Table 67: Global summary of serious adverse events reported within the 21-day (Days 0-20) post-vaccination period by age (TVC).

	Group							
	D-QIV		TIV-1		TIV-2		All	
	18-64y	65y+	18-64y	65y+	18-64y	65y+	18-64y	65y+
Number of subjects with at least one unsolicited symptom reported	5	11	2	4	0	1	7	16
Number of doses followed by at least one unsolicited symptom	5	11	2	4	0	1	7	16
Number of unsolicited symptoms classified by MedDRA Preferred Term*	5	13	2	4	0	1	7	18
Number of unsolicited symptoms reported	5	13	2	4	0	1	7	18

18-64y = Adults aged between 18 years to 64 years, 65y+ = Adults aged 65 years and older
* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once

Table 68: Global summary of serious adverse events reported during entire study period by age (TVC).

	Group							
	D-QIV		TIV-1		TIV-2		All	
	18-64y	65y+	18-64y	65y+	18-64y	65y+	18-64y	65y+
Number of subjects with at least one unsolicited symptom reported	20	50	5	21	0	1	25	72
Number of doses followed by at least one unsolicited symptom	20	50	5	21	0	1	25	72
Number of unsolicited symptoms classified by MedDRA Preferred Term*	20	78	5	22	0	1	25	101
Number of unsolicited symptoms reported	20	79	5	22	0	1	25	102

18-64y = Adults aged between 18 years to 64 years
65y+ = Adults aged 65 years and older
* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once

Analysis by Gender

A global summary of serious adverse events reported within the 21-day post-vaccination period by gender is presented in table 69 and a global summary of serious adverse events reported during the entire study period by gender is presented in table 70.

Table 69: Global summary of serious adverse events reported within the 21-day (Days 0-20) post-vaccination period by gender.

	Grou							
	D-QIV		TIV-1		TIV-2		All	
	Male	Female	Male	Female	Male	Female	Male	Female
Number of subjects with at least one unsolicited symptom reported	8	8	5	1	1	0	14	9
Number of doses followed by at least one unsolicited symptom	8	8	5	1	1	0	14	9
Number of unsolicited symptoms classified by MedDRA Preferred Term*	8	10	5	1	1	0	14	11
Number of unsolicited symptoms reported	8	10	5	1	1	0	14	11

* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once

Table 70: Global summary of serious adverse events reported during entire study period by gender.

	Group							
	D-QIV		TIV-1		TIV-2		All	
	Male	Female	Male	Female	Male	Female	Male	Female
Number of subjects with at least one unsolicited symptom reported	32	38	16	10	1	0	49	48
Number of doses followed by at least one unsolicited symptom	32	38	16	10	1	0	49	48
Number of unsolicited symptoms classified by MedDRA Preferred Term*	44	54	17	10	1	0	62	64
Number of unsolicited symptoms reported	45	54	17	10	1	0	63	64

* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once.

Analysis by Race

A global summary of serious adverse events reported within the 21-day post-vaccination period by race (White/Caucasian versus Non-White/Caucasian) is presented in table 71 and a global summary of serious adverse events reported during the entire study period by race is presented in table 72.

Table 71: Global Summary of serious adverse events reported within the 21-day (Days 0-20) post-vaccination period by race.

	Group							
	D-QIV		TIV-1		TIV-2		All	
	W/C	NW/C	W/C	NW/C	W/C	NW/C	WC	NW/C
Number of subjects with at least one unsolicited symptom reported	10	6	6	0	0	1	16	7
Number of unsolicited symptoms classified by MedDRA Preferred Term*	12	6	6	0	0	1	18	7
Number of unsolicited symptoms reported**	12	6	6	0	0	1	18	7

W/C = White/Caucasian subjects, NW/C = Non-White/Caucasian subjects

* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once

** Symptoms reported by a subject after a given dose and classified by the same Preferred Term and the same start date of the event, are counted once

Table 72: Global Summary of serious adverse events reported during the entire study period by race.

	Group							
	D-QIV		TIV-1		TIV-2		All	
	W/C	NW/C	W/C	NW/C	W/C	NW/C	WC	NW/C
Number of subjects with at least one unsolicited symptom reported	50	20	23	3	0	1	73	24
Number of unsolicited symptoms classified by MedDRA Preferred Term*	75	23	24	3	0	1	99	27
Number of unsolicited symptoms reported**	76	23	24	3	0	1	100	27

W/C = White/Caucasian subjects, NW/C = Non-White/Caucasian subjects

* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once

** Symptoms reported by a subject after a given dose and classified by the same Preferred Term and the same start date of the event, are counted once

Analysis by Region

A global summary of serious adverse events reported within the 21-day post-vaccination period by region is presented in table 73 and a global summary of serious adverse events reported during the entire study period by region is presented in table 74.

Table 73: Global Summary of serious adverse events reported within the 21-day (Days 0-20) post-vaccination period by region.

	Group											
	D-QIV			TIV-1			TIV-2			All		
	US	Europe	Asia	US	Europe	Asia	US	Europe	Asia	US	Europe	Asia
Number of subjects with at least one unsolicited symptom reported	5	6	5	2	4	0	0	0	1	7	10	6
Number of unsolicited symptoms classified by MedDRA Preferred Term*	5	8	5	2	4	0	0	0	1	7	12	6
Number of unsolicited symptoms reported**	5	8	5	2	4	0	0	0	1	7	12	6

US = Subjects from United States, Europe = Subjects from Germany, Romania and Spain

Asia = Subjects from Korea and Taiwan

* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once

** Symptoms reported by a subject after a given dose and classified by the same Preferred Term and the same start date of the event, are counted once

Table 74: Global Summary of serious adverse events reported during the entire study period by region.

	Group											
	D-QIV			TIV-1			TIV-2			All		
	US	Europe	Asia	US	Europe	Asia	US	Europe	Asia	US	Europe	Asia
Number of subjects with at least one unsolicited symptom reported	21	32	17	9	14	3	0	0	1	30	46	21
Number of unsolicited symptoms classified by MedDRA Preferred Term*	39	39	20	9	15	3	0	0	1	48	54	24
Number of unsolicited symptoms reported**	40	39	20	9	15	3	0	0	1	49	54	24

US = Subjects from United States, Europe = Subjects from Germany, Romania and Spain

Asia = Subjects from Korea and Taiwan

* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once

** Symptoms reported by a subject after a given dose and classified by the same Preferred Term and the same start date of the event, are counted once

***Reviewer's Comments**: In addition to the above subgroup analysis by the reviewer, CBER requested the applicant to conduct subgroup analysis by gender, race and region and applicant has submitted in depth descriptive sub group analysis of safety by gender, race, region and country in amendment 8 submitted to the BLA on August 16, 2012. Please refer to applicant's tables in amendment 8 for details of these analyses.*

3.1.4.3 Safety Conclusions

Within the 21 days post-vaccination period (Day 0-Day 20), **12.5%** of subjects from the D-QIV group, **13.7%** from the TIV-1 group and **15.1%** from the TIV-2 group experienced at least one unsolicited AE. In all 3 groups, nasopharngitis and cough were the most frequent unsolicited AE reported. At least one grade 3 unsolicited AE occurred in **1.3%** of subjects in the D-QIV group, **0.7%** in the TIV-1 group and **0.3%** in the TIV-2 group.

Within the 21 days post-vaccination period (Day 0-Day 20), **6.4%** of subjects from the D-QIV group, **5.9%** from the TIV-1 group and **7.7%** from the TIV-2 group experienced at least one unsolicited AE with medically attended visit.

During the entire study period, **22.7%** of the subjects in the D-QIV group and **21.4%** of the subjects in the TIV-1 group had unsolicited adverse events with medically attended visit. TIV-2 group was followed only up to 21 day post-vaccination period; therefore, the entire study period for the TIV-2 was approximately 21 days.

Overall, the percentage of subjects reporting SAEs is low; none of the SAEs reported was assessed as related to the vaccine by the investigators. Within the 21-day period, **0.5%** of subjects in the D-QIV group**, 0.6%** of subjects in the TIV-1 group and **0.2%** of subjects in the TIV-2 group reported at least one SAE.

During the entire study period, **2.3%** of subjects in the D-QIV group and **2.6%** of subjects in the TIV-1 group reported at least one SAE.

During the entire study period, fatal SAEs were reported for **9 (0.3%)** D-QIV subjects and **3(0.3%)** TIV-1 subjects; all were >65 years of age.

Injection site pain was the most frequently reported local AE across treatment groups. Fatigue, headache and muscle aches were the most frequently reported general AEs across the treatment groups. Grade 3 solicited local AEs were reported by less than **2.1%** of subjects and general AEs were reported by less than 1% in all treatments groups.

3.2 Study D-QIV-003

This study is a phase III, double-blind, randomized study to evaluate the immunogenicity and safety of GSK's quadrivalent influenza vaccine compared to GSK's trivalent influenza vaccine administered intramuscularly in children aged 3 to 17 years and to describe the safety and immunogenicity of GSK's quadrivalent influenza vaccine in children aged 6 to 35 months.

The study design is similar to study D-QIV-008 described above in section 3.1 of this review. The principal features of each study are summarized in table XX in section 1.2 of this review. Both studies evaluated the candidate D-QIV vaccine in adults (Study D-Qiv-008) and children from 3 years of age (Study D-Qiv-003). Both studies included two comparator groups, one receiving the trivalent influenza vaccine containing the strains recommended for the ongoing season, and one a second trivalent vaccine that contained a strain of the B lineage not included in the seasonal vaccine.

Study D-QIV-003 enrolled an additional group of 6 to 35-month old children for exploratory purposes. This group received open-label D-QIV vaccine.

Study Objectives:

Primary:- To evaluate the immunological non-inferiority (in terms of Geometric Mean Titer [GMT] and Seroconversion Rate [SCR]) of D-QIV versus TIV-1 (*Fluarix*) and TIV-2 in children (3 to 17 years) at 28 days (primed subjects) or 56 days (unprimed subjects) following first vaccination (28 days after completion of the immunization series).

Secondary:

- To evaluate the immunological superiority (in terms of GMTs and SCR) of D-QIV versus TIV-1 (*Fluarix*) and TIV-2 in children (3 to 17 years) at 28 days (primed subjects) or 56 days (unprimed subjects) following first vaccination (28 days after completion of the immunization series) for the B strain not contained in each TIV formulation.
- To describe the immunogenicity (in terms of GMT, seroprotection rate [SPR], SCR and mean geometric increase [MGI]) of D-QIV, TIV-1(*Fluarix*) and TIV-2 for all subjects, and of D-QIV for the 6 to 35 months age group.
- To evaluate the safety and reactogenicity of D-QIV, TIV-1 (*Fluarix*) and TIV-2 in the 3 to 17 years age category and to evaluate the safety and reactogenicity of D-QIV for the 6 to 35 months age group.

Evaluation criteria for the study objectives are the same as study D-QIV-008 described in section 3.1 above.

Study Endpoints

Primary endpoint:
Humoral immune response in terms of HI antibodies

- Serum anti-HA antibody titers against the four vaccine strains at Day 0 and 28 days after last vaccine dose in each group were used to calculate:
  - GMTs of HI antibody titers at Day 0 and 28 days after last vaccine dose in each group.
  - SCR 28 days after last vaccine dose.

Secondary endpoint
Immunology:
Humoral immune response in terms of HI antibodies.

- Serum anti-HA antibody titers against the four vaccine strains at Day 0 and 28 days after last vaccine dose in each group stratified by age (6 to 35 months, 3 to 8 years and 9 to 17 years) were used to calculate:
  - GMTs of HI antibody titers at Day 0 and 28 days after last vaccine dose.
  - SCR for the three strains 28 days after last vaccination.
  - SPR at Day 0 and 28 days after last vaccine dose.
  - MGI 28 days after last vaccine dose.

Safety:

- Solicited local AEs
  - Occurrence, duration and intensity during a 7-day follow-up period (i.e. day of vaccination and 6 subsequent days) after each 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 each vaccination, in each group.

- Unsolicited AEs
  - Occurrence, intensity and relationship to vaccination during a 28-day follow-up period (i.e. day of vaccination and 27 subsequent days) after each vaccination, in each group.
- SAEs and pIMDs
  - Occurrence and relationship to vaccination during the entire study period in each group.
- AEs that led to a MAV
  - Occurrence, intensity and relationship to vaccination during the entire study period in each group.

Statistical Analysis Methods

Refer to section 3.1.1.3 above.

3.2.2 Study Population Results

Number of subjects:
Table 75 below presents the planned and enrolled number of subjects in the study

Table 75: Number of planned, enrolled and completed subjects in study D-QIV-003

Study group	Age (Min/Max)	Number of Subjects		
		Planned	Enrolled	Completed
D-QIV	3- 17 years	900	915	891
TIV-1 (Fluarix)	3 - 17 years	900	914	880
TIV-2	3 - 17 years	900	912	886
D-QIV	6 - 35 months	300	277	276

Study completion and withdrawal from study

The numbers of subjects vaccinated, completed and withdrawn are presented in table 76 and reason of withdrawal in table 77 below.

Table 76: Number of subjects vaccinated, completed and withdrawn (TVC)

	D-QIV	TIV-1 (Fluarix)	TIV-2	D-QIV-Y	Total
Number of subjects vaccinated	915	912	911	277	3015
Number of subjects completed	891	880	886	276	2933
Number of subjects withdrawn	24	32	25	1	82

Table 77: Number of subjects withdrawn with reason of withdrawal by study group

Reason of withdrawal	D-QIV	TIV-1	TIV-2	D-QIV-Y	Total
Serious Adverse Event	1	1	0	0	2
Non-Serious Adverse Event	0	1	0	0	1
Consent withdrawal (not due to AE)	5	1	4	0	10
Migrated/moved from study area	1	2	0	0	3
Lost to follow up (subjects with incomplete vaccination course)	3	3	3	0	9
Lost to follow up (subjects with complete vaccination course)	12	24	18	1	55
Other- Not reachable by phone	1	0	0	0	1

Overall, 2933 subjects completed the study and 82 subjects withdrew. Two subjects, one from the D-QIV and one from the Fluarix group, discontinued the study due to a SAE. None of these were considered as related to vaccination.

3.2.3 Immunogenicity Results

The analysis of immunogenicity was performed on the ATP immunogenicity cohort (primary analysis).

3.2.3.1 Primary Immunogenicity Objective

For GMT Ratios:

- The upper limit of the two-sided 95% CI for the GMT ratio of TIV (pooling Fluarix and TIV-2) over D-QIV was **1.15** for A/California/7/2009 (H1N1) strain and **1.05** for A/Victoria/210/2009 (H3N2) strain, which did not exceed 1.5;
- The upper limit of two-sided 95% CI for the GMT ratio for Fluarix over D-QIV for B/Brisbane/60/2008 (Victoria lineage) strain was **1.09**, which did not exceed 1.5;
- The upper limit of two-sided 95% CI for the GMT ratio for TIV-2 over D-QIV for B/Brisbane/3/2007 (Yamagata lineage) strain was **1.18**, which did not exceed 1.5

For the difference in SCR:

- The upper limit of the two-sided 95% CI for the difference in SCR of TIV (pooling Fluarix and TIV-2) minus D-QIV was **1.86%** for A/California/7/2009 (H1N1) strain and **2.86%** for A/Victoria/210/2009 (H3N2) strain, which did not exceed 10%;
- The upper limit of two-sided 95% CI for the difference in SCR for Fluarix minus D-QIV for B/Brisbane/60/2008 (Victoria lineage) strain was **2.98%**, which did not exceed 10%;
- The upper limit of two-sided 95% CI for the difference in SCR for TIV-2 minus D-QIV for B/Brisbane/3/2007 (Yamagata lineage) strain was **2.65%**, which did not exceed 10%.

The non-inferiority results (D-QIV versus TIV-1 (*Fluarix*) and TIV-2) at 28 days after last vaccination in terms of GMTs are presented in the following tables: Table 78 for the two A strains, table 79 for the B/Victoria strain and table 80 for the B/Yamagata strain.

Table 78: Non-inferiority of D-QIV versus TIV (Fluarix & TIV-2) in terms of GMTs

(adjusted GMT ratio) at day 28 after the last vaccination for the two A strains (ATP cohort)

					Adjusted GMT ratio (TIV / D-QIV)		
	TIV		D-QIV			95% CI	
Anti body	N	Adjusted GMT	N	Adjusted GMT	Value	LL	UL
A/California/7/2009 (H1N1) (1/DIL)	1618	423.6	790	398.4	1.06	0.98	1.15
A/Victoria/210/2009 (H3N2) (1/DIL)	1618	228.7	790	232.9	0.98	0.92	1.05

D-QIV = Subjects of 3-17 years received D-QIV, TIV = Subjects of 3-17 years received either TIV-1 (*Fluarix*) or TIV-2
Adjusted GMT = geometric mean antibody titer adjusted for baseline titer
N = Number of subjects with both pre- and post-vaccination results available

Table 79: Non-inferiority of D-QIV versus Fluarix in terms of GMTs (adjusted GMT ratio) at day 28 after the last vaccination for B-Victoria strain (ATP cohort)

					Adjusted GMT ratio (FLUARIX / D-QIV)		
	FLUARIX		D-QIV			95% CI	
Antibody	N	Adjusted GMT	N	Adjusted GMT	Value	LL	UL
B/Brisbane/60/2008 (Victoria) (1/DIL)	818	245.4	790	245.2	1.00	0.92	1.09

D-QIV = Subjects of 3-17 years received D-QIV, TIV = Subjects of 3-17 years received either TIV-1 (*Fluarix*) or TIV-2
Adjusted GMT = geometric mean antibody titer adjusted for baseline titer
N = Number of subjects with both pre- and post-vaccination results available

Table 80: Non-inferiority of D-QIV versus TIV-2 in terms of GMTs (adjusted GMT ratio) at day 28 after the last vaccination for B-Yamagata strain (ATP cohort)

					Adjusted GMT ratio (TIV-2 / D-QIV)		
	TIV-2		D-QIV			95% CI	
Antibody	N	Adjusted GMT	N	Adjusted GMT	Value	LL	UL
B/Brisbane/3/2007 (Yamagata) (1/DIL)	800	635.3	790	581.1	1.09	1.01	1.18

D-QIV = Subjects of 3-17 years received D-QIV, TIV = Subjects of 3-17 years received either TIV-1 (*Fluarix*) or TIV-2
Adjusted GMT = geometric mean antibody titer adjusted for baseline titer
N = Number of subjects with both pre- and post-vaccination results available

The non-inferiority of FLU D-QIV versus TIV-1 (*Fluarix*) and TIV-2 at 28 days after last vaccination in terms of SCRs is presented in table 81for the two A strains, in table 82 for the B/Victoria strain and in table 83 for the B/Yamagata strain.

Table 81: Non-inferiority of D-QIV versus TIV (Fluarix & TIV-2) in terms of

seroconversion rate (difference in seroconversion rate) at day 28 after the last vaccination for the two A strains (ATP cohort)

							Difference in seroconversion rate (TIV minus D-QIV)		
	TIV			D-QIV				95% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
A/California/7/2009 (H1N1) (1/DIL)	1618	1468	90.7	790	722	91.4	-0.66	-2.99	1.86
A/Victoria/210/2009 (H3N2) (1/DIL)	1618	1153	71.3	790	571	72.3	-1.02	-4.78	2.86

D-QIV = Subjects of 3-17 years received D-QIV, TIV = Subjects of 3-17 years received either TIV-1 (*Fluarix*) or TIV-2
Vaccine response defined as:

- For initially seronegative subjects: post-vaccination antibody titer ≥ 40 1/DIL at POST
- For initially seropositive subjects: antibody titer at POST ≥4 fold the pre-vaccination antibody titer

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with a vaccine response

Table 82: Non-inferiority of D-QIV versus Fluarix in terms of seroconversion rate (difference in seroconversion rate) at day 28 after the last vaccination for B-Victoria strain (ATP cohort)

							Difference in seroconversion rate (FLUARIX minus D-QIV)		
	FLUARIX			D-QIV				95% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
B/Brisbane/60/2008 (Victoria) (1/DIL)	818	560	68.5	790	553	70.0	-1.54	-6.05	2.98

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received TIV-1 (*Fluarix*)
Vaccine response defined as:

- For initially seronegative subjects: post-vaccination antibody titer ≥ 40 1/DIL at POST
- For initially seropositive subjects: antibody titer at POST ≥ 4 fold the pre-vaccination antibody titer

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with a vaccine response

Table 83:Non-inferiority of D-QIV versus TIV-2 in terms of seroconversion rate (difference in seroconversion rate) at day 28 after the last vaccination for B-Yamagata strain (ATP cohort)

							Difference in seroconversion rate (TIV-2 minus D-QIV)		
	TIV-2			D-QIV				95% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
B/Brisbane/3/2007 (Yamagata) (1/DIL)	800	566	70.8	790	573	72.5	-1.78	-6.21	2.65

D-QIV = Subjects of 3-17 years received D-QIV, TIV-2 = Subjects of 3-17 years received TIV-2
Vaccine response defined as:

- For initially seronegative subjects: post-vaccination antibody titer ≥ 40 1/DIL at POST
- For initially seropositive subjects: antibody titer at POST ≥ 4 fold the pre-vaccination antibody titer

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with a vaccine response

All the results in tables 78-83 indicate that the pre-specified criteria of immunological non-inferiority of D-QIV versus TIV-1 (*Fluarix*) and TIV-2 in children 3 to 17 years old, at 28 days

after last vaccination in terms of GMT ratios and SCR differences for the concerned strains were met.

3.2.3.2 Secondary Immunogenicity Objective

Superiority of D-QIV versus TIV formulations

The superiority of D-QIV versus TIV-1 (*Fluarix*) or TIV-2 in children 3 to 17 years old, at 28 days after last vaccination in terms of GMTs is presented in table 84 for the B/Brisbane/3/2007 (Yamagata lineage) strain and in table 85 for the B/Brisbane/60/2008 (Victoria lineage) strain.

Table 84: Superiority of D-QIV versus Fluarix in terms of GMTs (adjusted GMT ratio) at day 28 after the last vaccination for B-Yamagata strain (ATP)

					Adjusted GMT ratio (D-QIV / FLUARIX)		
	D-QIV		FLUARIX			95% CI	
Antibody	N	Adjusted GMT	N	Adjusted GMT	Value	LL	UL
B/Brisbane/3/2007 (Yamagata) (1/DIL)	790	572.4	818	224.6	2.55	2.36	2.75

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received TIV-1 (*Fluarix*)
Adjusted GMT = geometric mean antibody titer adjusted for baseline titer
N = Number of subjects with both pre- and post-vaccination results available

The lower limit of the two-sided 95% CI for the GMT ratio for D-QIV over Fluarix for B/Brisbane/3/2007 (Yamagata lineage) strain was **2.36**, which is greater than 1 (the pre-specified superiority criterion).

Table 85: Superiority of D-QIV versus TIV-2 in terms of GMTs (adjusted GMT ratio) at day 28 after the last vaccination for B-Victoria strain (ATP)

					Adjusted GMT ratio (D-QIV / TIV-2)		
	D-QIV		TIV-2			95% CI	
Antibody	N	Adjusted GMT	N	Adjusted GMT	Value	LL	UL
B/Brisbane/60/2008 (Victoria) (1/DIL)	790	249.2	800	86.9	2.87	2.63	3.13

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received TIV-1 (*Fluarix*)
Adjusted GMT = geometric mean antibody titer adjusted for baseline titer
N = Number of subjects with both pre- and post-vaccination results available

The lower limit of the two-sided 95% CI for the GMT ratio of D-QIV over TIV-2 for B/Brisbane/60/2008 (Victoria lineage) strain was **2.63**, which is greater than 1 (the pre-specified superiority criterion).

The superiority of FLU D-QIV versus TIV-1 (*Fluarix*) or TIV-2 in children 3 to 17 years old, at 28 days after last vaccination in terms of SCRs is presented in table 86 for the B/Brisbane/3/2007 (Yamagata lineage) strain and in table 87 for the B/Brisbane/60/2008 (Victoria lineage) strain.

Table 86: Superiority of D-QIV versus Fluarix in terms of seroconversion rate (difference in seroconversion rate) at day 28 after the last vaccination for B-Yamagata strain (ATP cohort)

							Difference in seroconversion rate (D-QIV minus FLUARIX)		
	D-QIV			FLUARIX				95% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
B/Brisbane/3/2007 (Yamagata) (1/DIL)	790	573	72.5	818	303	37.0	35.49	30.87	39.95

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received TIV-1 (*Fluarix*)
Vaccine response defined as:

- For initially seronegative subjects: post-vaccination antibody titer ≥ 40 1/DIL at POST
- For initially seropositive subjects: antibody titer at POST ≥ 4 fold the pre-vaccination antibody titer

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with a vaccine response

The lower limit of the two-sided 95% CI for the difference in SCR for D-QIV over Fluarix for B/Brisbane/3/2007 (Yamagata lineage) strain was **30.87%**, which is greater than 0% (the pre-specified superiority criterion).

Table 87: Superiority of D-QIV versus TIV-2 in terms of seroconversion rate (difference in seroconversion rate) at day 28 after the last vaccination for B-Victoria strain (ATP cohort)

							Difference in seroconversion rate (D-QIV minus TIV-2)		
	D-QIV			TIV-2				95% CI	
Antibody	N	n	%	N	n	%	%	LL	UL
B/Brisbane/60/2008 (Victoria) (1/DIL)	790	553	70.0	800	237	29.6	40.38	35.78	44.77

D-QIV = Subjects of 3-17 years received D-QIV, TIV-2 = Subjects of 3-17 years received TIV-2
Vaccine response defined as:

- For initially seronegative subjects: post-vaccination antibody titer ≥ 40 1/DIL at POST
- For initially seropositive subjects: antibody titer at POST ≥ 4 fold the pre-vaccination antibody titer

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with a vaccine response

The lower limit of the two-sided 95% CI for the difference in SCR of D-QIV over TIV-2 for B/Brisbane/60/2008 (Victoria lineage) strain was **35.78%**, which is greater than 0% (the pre-specified superiority criterion).

The immunological superiority of D-QIV versus TIV-1 (*Fluarix*) and TIV-2 in children aged 3 to 17 years, at 28 days after last vaccination met the pre-specified criterion for superiority in terms of GMT ratios and SCR differences for the B strain that is not contained in each TIV formulation.

Humoral Immune Response

The geometric mean titers (GMTs), seropositivity rates and seroprotection rate (SPR) with 95% CI measured on Days 0 and 28 days after last vaccination and the seroconversion rates (SCRs) and mean geometric increase (MGIs) measured 28 days after last vaccination for the DQIV, Fluarix, TIV-2 and D-QIV Young groups are presented in table 88.

Seropositivity rates:
For subjects 3 to 17 years old post-vaccination: more than 99.4% of subjects in each group were seropositive for the four strains.
For subjects 6 to 35 months old receiving D-QIV (D-QIV Young group) post-vaccination: 97.0%, 99.1%, 97.0% and 100% of the subjects were seropositive for the A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage) and B/Brisbane/3/2007 (Yamagata lineage) strain, respectively.

Table 88: HI antibodies against the four strains in terms of seropositivity, GMTs, SCR, SPR and MGI (ATP cohort)

			≥ 10 1/DIL			GMT			SCR			SPR			MGI		
				95% CI			95% CI			95% CI			95% CI			95% CI	
Group	Timing	N	%	LL	UL	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
A/California/7/2009 (H1N1)																	
D-QIV	PRE	790	64.7	61.2	68.0	21.6	19.7	23.7	-	-	-	43.4	39.9	47.0	-	-	-
	POST	791	99.9	99.3	100	386.2	357.3	417.4	91.4	89.2	93.3	96.6	95.1	97.7	18.0	16.6	19.5
FLUARIX	PRE	819	68.9	65.6	72.0	24.9	22.8	27.3	-	-	-	49.3	45.9	52.8	-	-	-
	POST	818	99.4	98.6	99.8	433.2	401.0	468.0	89.9	87.6	91.8	96.9	95.5	98.0	17.4	16.0	18.8
TIV-2	PRE	800	63.5	60.1	66.8	22.1	20.1	24.2	-	-	-	44.1	40.6	47.6	-	-	-
	POST	801	99.6	98.9	99.9	422.3	390.5	456.5	91.6	89.5	93.5	97.1	95.7	98.2	19.2	17.7	20.9
D-QIV-Y	PRE	232	31.0	25.1	37.4	12.3	10.2	14.8	-	-	-	25.9	20.4	32.0	-	-	-
	POST	234	97.0	93.9	98.8	140.0	113.7	172.3	78.0	72.1	83.2	79.9	74.2	84.9	11.7	10.2	13.4
A/Victoria/210/2009 (H3N2)																	
D-QIV	PRE	790	79.6	76.6	82.4	29.0	26.6	31.6	-	-	-	48.2	44.7	51.8	-	-	-
	POST	791	99.9	99.3	100	228.8	215.0	243.4	72.3	69.0	75.4	98.0	96.7	98.8	7.9	7.3	8.6
FLUARIX	PRE	819	82.2	79.4	84.7	31.4	28.8	34.2	-	-	-	50.3	46.8	53.8	-	-	-
	POST	818	99.8	99.1	100	227.3	213.3	242.3	70.7	67.4	73.8	97.8	96.5	98.7	7.2	6.7	7.8
TIV-2	PRE	800	79.1	76.1	81.9	31.2	28.6	34.2	-	-	-	51.1	47.6	54.6	-	-	-
	POST	801	99.9	99.3	100	234.0	219.1	249.9	71.9	68.6	75.0	96.5	95.0	97.7	7.5	6.9	8.1
D-QIV-Y	PRE	232	22.0	16.8	27.9	8.6	7.4	9.9	-	-	-	14.7	10.4	19.9	-	-	-
	POST	234	99.1	96.9	99.9	87.5	73.8	103.7	68.5	62.1	74.5	72.2	66.0	77.9	10.4	9.0	11.9
B/Brisbane/60/2008 (Victoria)																	
D-QIV	PRE	790	78.4	75.3	81.2	30.9	28.2	33.9	-	-	-	48.2	44.7	51.8	-	-	-
	POST	791	100	99.5	100	244.2	227.5	262.1	70.0	66.7	73.2	97.3	96.0	98.3	7.9	7.3	8.6
FLUARIX	PRE	819	78.0	75.0	80.8	31.0	28.2	34.0	-	-	-	48.4	44.9	51.8	-	-	-
	POST	818	99.8	99.1	100	245.6	229.2	263.2	68.5	65.2	71.6	96.6	95.1	97.7	7.9	7.2	8.6
TIV-2	PRE	800	78.5	75.5	81.3	33.2	30.2	36.6	-	-	-	49.9	46.4	53.4	-	-	-
	POST	801	97.9	96.6	98.8	88.4	81.5	95.8	29.6	26.5	32.9	79.8	76.8	82.5	2.7	2.5	2.9
D-QIV-Y	PRE	232	30.6	24.7	37.0	9.0	7.9	10.4	-	-	-	12.1	8.2	17.0	-	-	-
	POST	234	97.0	93.9	98.8	86.4	72.6	102.9	68.1	61.7	74.1	71.4	65.1	77.1	9.7	8.5	11.2
B/Brisbane/3/2007 (Yamagata)																	
D-QIV	PRE	790	92.9	90.9	94.6	77.3	70.0	85.3	-	-	-	71.5	68.2	74.6	-	-	-
	POST	791	100	99.5	100	569.6	533.6	608.1	72.5	69.3	75.6	99.2	98.4	99.7	7.4	6.8	8.0
FLUARIX	PRE	819	92.1	90.0	93.8	77.2	70.0	85.2	-	-	-	70.2	66.9	73.3	-	-	-
	POST	818	99.9	99.3	100	224.7	207.9	242.9	37.0	33.7	40.5	94.4	92.6	95.9	2.9	2.7	3.1
TIV-2	PRE	800	92.3	90.2	94.0	84.7	76.6	93.6	-	-	-	74.1	70.9	77.1	-	-	-
	POST	801	100	99.5	100	643.3	603.2	686.1	70.8	67.5	73.9	99.6	98.9	99.9	7.6	7.0	8.3
D-QIV-Y	PRE	232	53.4	46.8	60.0	13.1	11.4	15.2	-	-	-	20.7	15.7	26.5	-	-	-
	POST	234	100	98.4	100	167.7	144.1	195.3	82.3	76.8	87.0	90.6	86.1	94.0	12.9	11.0	15.3

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received TIV-1 (*Fluarix*)
TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV
N = Number of subjects with pre- and post-vaccination results available
PRE = Pre-vaccination at Day 0 / POST = Post-vaccination at 28 days after the last vaccination
GMT = geometric mean antibody titer calculated on all subjects
Seroconversion defined as: - For initially seronegative subjects, antibody titer ≥ 40 1/DIL after vaccination
- For initially seropositive subjects, antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer
MGI = Mean Geometric increase in serum HI GMTs post-vaccination
SPR = percentage of vaccinees with serum H1N1 HI antibody titer ≥ 1:40

3.2.3.3 Subgroup Analysis of Immunogenicity

Analysis by Age

Seropositivity rates and GMTs, SCRs, SPRs and MGIs analyzed by age strata are presented in tables 89 to 92 respectively.

Table 89: **Seropositivity rates and GMTs for HI antibody titers at day 0 and day 28 or day 56 – by age strata (ATP cohort)**

					≥ 10 1/DIL				GMT		
							95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL
A/California/7/2009 (H1N1)	D-QIV	3 - 8 years	PRE	488	296	60.7	56.2	65	20.7	18.3	23.3
			POST	489	488	99.8	98.9	100	353.4	320	390.3
		9 - 17 years	PRE	302	215	71.2	65.7	76.2	23.2	20.2	26.6
			POST	302	302	100	98.8	100	445.8	394	504.7
	FLUARIX	3 - 8 years	PRE	511	330	64.6	60.3	68.7	22.2	19.8	24.9
			POST	510	505	99	97.7	99.7	382.1	345	422.7
		9 - 17 years	PRE	308	234	76	70.8	80.6	30.2	26.1	34.9
			POST	308	308	100	98.8	100	533.3	475	599
	TIV-2	3 - 8 years	PRE	503	311	61.8	57.4	66.1	22.4	19.8	25.3
			POST	504	501	99.4	98.3	99.9	381.3	345	421.5
		9 - 17 years	PRE	297	197	66.3	60.6	71.7	21.5	18.6	24.8
			POST	297	297	100	98.8	100	502	444	567.5
	D-QIV-Y	6 - 7 months	PRE	70	8	11.4	5.1	21.3	7.1	5.5	9.1
			POST	71	66	93	84.3	97.7	56.2	39.9	79.2
		18 - 35 months	PRE	162	64	39.5	31.9	47.5	15.6	12.3	19.8
			POST	163	161	98.8	95.6	99.9	208.3	165	263.4
A/Victoria/210/2009 (H3N2)	D-QIV	3 - 8 years	PRE	488	363	74.4	70.3	78.2	29.3	26.1	32.9
			POST	489	489	100	99.2	100	245.5	226	266.2
		9 - 17 years	PRE	302	266	88.1	83.9	91.5	28.5	25.1	32.3
			POST	302	301	99.7	98.2	100	204.1	186	224.5
	FLUARIX	3 - 8 years	PRE	511	398	77.9	74	81.4	32.9	29.2	37
			POST	510	509	99.8	98.9	100	242	223	262.8
		9 - 17 years	PRE	308	275	89.3	85.3	92.5	29	25.8	32.7
			POST	308	307	99.7	98.2	100	204.9	185	226.6
	TIV-2	3 - 8 years	PRE	503	374	74.4	70.3	78.1	31.5	28	35.5
			POST	504	503	99.8	98.9	100	244.4	224	266.5
		9 - 17 years	PRE	297	259	87.2	82.9	90.8	30.8	27	35.1
			POST	297	297	100	98.8	100	217.5	197	240.2
	D-QIV-Y	6 - 7 months	PRE	70	6	8.6	3.2	17.7	6.2	5.1	7.6
			POST	71	69	97.2	90.2	99.7	43.8	33.7	57
		18 - 35 months	PRE	162	45	27.8	21	35.3	9.8	8.1	11.9
			POST	163	163	100	97.8	100	118.2	96.8	144.4
	D-QIV	3 - 8 years	PRE	488	354	72.5	68.4	76.5	27.1	24	30.6
			POST	489	489	100	99.2	100	236.3	215	259.2
		9 - 17 years	PRE	302	265	87.7	83.5	91.2	38.3	33.4	43.9
			POST	302	302	100	98.8	100	257.5	231	287.5

					≥ 10 1/DIL				GMT		
							95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL
B/Brisbane/60/2008 (Victoria)	FLUARIX	3 - 8 years	PRE	511	359	70.3	66.1	74.2	25.1	22.3	28.3
			POST	510	508	99.6	98.6	100	222.3	203	243.7
		9 - 17 years	PRE	308	280	90.9	87.1	93.9	43.9	38.2	50.6
			POST	308	308	100	98.8	100	289.8	262	320.4
	TIV-2	3 - 8 years	PRE	503	362	72	67.8	75.9	27.9	24.6	31.6
			POST	504	490	97.2	95.4	98.5	79.2	71.2	88.2
		9 - 17 years	PRE	297	266	89.6	85.5	92.8	44.7	38.6	51.7
			POST	297	294	99	97.1	99.8	106.4	94.6	119.8
	D-QIV-Y	6 - 7 months	PRE	70	10	14.3	7.1	24.7	5.9	5.3	6.6
			POST	71	66	93	84.3	97.7	40.2	31.2	51.6
		18 - 35 months	PRE	162	61	37.7	30.2	45.6	10.8	9	13.1
			POST	163	161	98.8	95.6	99.9	120.7	98.2	148.4
B/Brisbane/3/2007 (Yamagata)	D-QIV	3 - 8 years	PRE	488	440	90.2	87.2	92.7	54.9	48.7	61.9
			POST	489	489	100	99.2	100	481.3	443	522.8
		9 - 17 years	PRE	302	294	97.4	94.8	98.8	134.3	115	156.5
			POST	302	302	100	98.8	100	748.1	677	826.8
	FLUARIX	3 - 8 years	PRE	511	448	87.7	84.5	90.4	51.9	45.9	58.7
			POST	510	509	99.8	98.9	100	163.5	148	180.1
		9 - 17 years	PRE	308	306	99.4	97.7	99.9	149.3	130	171.1
			POST	308	308	100	98.8	100	380.6	342	423.4
	TIV-2	3 - 8 years	PRE	503	448	89.1	86	91.7	57.6	50.9	65.1
			POST	504	504	100	99.3	100	566.7	523	614.1
		9 - 17 years	PRE	297	290	97.6	95.2	99	162.8	140	188.6
			POST	297	297	100	98.8	100	797.9	720	885
	D-QIV-Y	6 - 7 months	PRE	70	27	38.6	27.2	51	10	7.9	12.7
			POST	71	71	100	94.9	100	93.5	73.5	119
		18 - 35 months	PRE	162	97	59.9	51.9	67.5	14.8	12.4	17.7
			POST	163	163	100	97.8	100	216.3	181	258.7

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received TIV-1 (*Fluarix*)
TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titer within the specified range
PRE = Pre-vaccination at Day 0, POST = Post-vaccination at 28 days after the last vaccination

Reviewer's comment

The descriptive analyses of the seropositivity rates and GMT show similar results in all age groups.

Table 90: Seroconversion rate for HI antibody titers at day 28 or 56 by age strata (ATP cohort)

				SCR			
						95% CI	
Strain	Group	Sub-group	N	n	%	LL	UL
A/California/7/2009 (H1N1)	D-QIV	3 - 8 years	488	447	91.6	88.8	93.9
		9 - 17 years	302	275	91.1	87.3	94.0
	FLUARIX	3 - 8 years	510	468	91.8	89.0	94.0
		9 - 17 years	308	267	86.7	82.4	90.3
	TIV-2	3 - 8 years	503	457	90.9	88.0	93.2
		9 - 17 years	297	276	92.9	89.4	95.6
	D-QIV-Y	6 - 17 months	70	43	61.4	49.0	72.8
		18 - 35 months	162	138	85.2	78.8	90.3
A/Victoria/210/2009 (H3N2)	D-QIV	3 - 8 years	488	367	75.2	71.1	79.0
		9 - 17 years	302	204	67.5	62.0	72.8
	FLUARIX	3 - 8 years	510	365	71.6	67.4	75.4
		9 - 17 years	308	213	69.2	63.7	74.3

				SCR			
						95% CI	
Strain	Group	Sub-group	N	n	%	LL	UL
	TIV-2	3 - 8 years	503	376	74.8	70.7	78.5
		9 - 17 years	297	199	67.0	61.3	72.3
	D-QIV-Y	6 - 17 months	70	37	52.9	40.6	64.9
		18 - 35 months	162	122	75.3	67.9	81.7
B/Brisbane/60/2008 (Victoria)	D-QIV	3 - 8 years	488	364	74.6	70.5	78.4
		9 - 17 years	302	189	62.6	56.9	68.1
	FLUARIX	3 - 8 years	510	367	72.0	67.8	75.8
		9 - 17 years	308	193	62.7	57.0	68.1
	TIV-2	3 - 8 years	503	154	30.6	26.6	34.8
		9 - 17 years	297	83	27.9	22.9	33.4
	D-QIV-Y	6 - 17 months	70	36	51.4	39.2	63.6
		18 - 35 months	162	122	75.3	67.9	81.7
B/Brisbane/3/2007 (Yamagata)	D-QIV	3 - 8 years	488	376	77.0	73.1	80.7
		9 - 17 years	302	197	65.2	59.6	70.6
	FLUARIX	3 - 8 years	510	203	39.8	35.5	44.2
		9 - 17 years	308	100	32.5	27.3	38.0
	TIV-2	3 - 8 years	503	403	80.1	76.4	83.5
		9 - 17 years	297	163	54.9	49.0	60.6
	D-QIV-Y	6 - 17 months	70	52	74.3	62.4	84.0
		18 - 35 months	162	139	85.8	79.5	90.8

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received TIV-1 (*Fluarix*)
TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV
Seroconversion defined as:

- For initially seronegative subjects, antibody titer ≥ 40 1/DIL after vaccination
- For initially seropositive subjects, antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer

N = number of subjects with pre and post-vaccination results available, n/% = number/percentage of seroconverted subjects

Table 91: Seroprotection rates (HI titer ≥ 80) for HI antibody titers at day 0 and day 28 or 56 by age strata (ATP cohort)

					SPR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
A/California/7/2009 (H1N1)	D-QIV	3 - 8 years	PRE	488	130	26.6	22.8	30.8
			POST	489	453	92.6	90.0	94.8
		9 - 17 years	PRE	302	71	23.5	18.8	28.7
			POST	302	279	92.4	88.8	95.1
	FLUARIX	3 - 8 years	PRE	511	128	25.0	21.3	29.0
			POST	510	471	92.4	89.7	94.5
		9 - 17 years	PRE	308	90	29.2	24.2	34.6
			POST	308	292	94.8	91.7	97.0
	TIV-2	3 - 8 years	PRE	503	141	28.0	24.1	32.2
			POST	504	464	92.1	89.3	94.3
		9 - 17 years	PRE	297	61	20.5	16.1	25.6
			POST	297	280	94.3	91.0	96.6
	D-QIV-Y	6 - 17 months	PRE	70	6	8.6	3.2	17.7
			POST	71	31	43.7	31.9	56.0
		18 - 35 months	PRE	162	43	26.5	19.9	34.0
			POST	163	124	76.1	68.8	82.4
A/Victoria/210/2009 (H3N2)	D-QIV	3 - 8 years	PRE	488	156	32.0	27.8	36.3
			POST	489	446	91.2	88.3	93.6
		9 - 17 years	PRE	302	72	23.8	19.1	29.1
			POST	302	275	91.1	87.3	94.0

					SPR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
	FLUARIX	3 - 8 years	PRE	511	177	34.6	30.5	38.9
			POST	510	462	90.6	87.7	93.0
		9 - 17 years	PRE	308	68	22.1	17.6	27.1
			POST	308	286	92.9	89.4	95.5
	TIV-2	3 - 8 years	PRE	503	190	37.8	33.5	42.2
			POST	504	446	88.5	85.4	91.1
		9 - 17 years	PRE	297	77	25.9	21.0	31.3
			POST	297	275	92.6	89.0	95.3
	D-QIV-Y	6 - 17 months	PRE	70	4	5.7	1.6	14.0
			POST	71	18	25.4	15.8	37.1
		18 - 35 months	PRE	162	23	14.2	9.2	20.5
			POST	163	107	65.6	57.8	72.9
B/Brisbane/60/2008 (Victoria)	D-QIV	3 - 8 years	PRE	488	145	29.7	25.7	34.0
			POST	489	430	87.9	84.7	90.7
		9 - 17 years	PRE	302	99	32.8	27.5	38.4
			POST	302	278	92.1	88.4	94.8
	FLUARIX	3 - 8 years	PRE	511	140	27.4	23.6	31.5
			POST	510	441	86.5	83.2	89.3
		9 - 17 years	PRE	308	118	38.3	32.9	44.0
			POST	308	292	94.8	91.7	97.0
	TIV-2	3 - 8 years	PRE	503	150	29.8	25.9	34.0
			POST	504	286	56.7	52.3	61.1
		9 - 17 years	PRE	297	119	40.1	34.4	45.9
			POST	297	202	68.0	62.4	73.3
	D-QIV-Y	6 - 17 months	PRE	70	0	0.0	0.0	5.1
			POST	71	25	35.2	24.2	47.5
		18 - 35 months	PRE	162	18	11.1	6.7	17.0
			POST	163	115	70.6	62.9	77.4
B/Brisbane/3/2007 (Yamagata)	D-QIV	3 - 8 years	PRE	488	233	47.7	43.2	52.3
			POST	489	480	98.2	96.5	99.2
		9 - 17 years	PRE	302	221	73.2	67.8	78.1
			POST	302	299	99.0	97.1	99.8
	FLUARIX	3 - 8 years	PRE	511	227	44.4	40.1	48.9
			POST	510	395	77.5	73.6	81.0
		9 - 17 years	PRE	308	235	76.3	71.1	80.9
			POST	308	297	96.4	93.7	98.2
	TIV-2	3 - 8 years	PRE	503	248	49.3	44.9	53.8
			POST	504	493	97.8	96.1	98.9
		9 - 17 years	PRE	297	228	76.8	71.5	81.5
			POST	297	291	98.0	95.7	99.3
	D-QIV-Y	6 - 17 months	PRE	70	4	5.7	1.6	14.0
			POST	71	43	60.6	48.3	72.0
		18 - 35 months	PRE	162	20	12.3	7.7	18.4
			POST	163	132	81.0	74.1	86.7

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received TIV-1 (*Fluarix*)
TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV
N = Number of subjects with available results
n/% = Number/percentage of seroprotected subjects (HI titer ≥ 80 1/DIL)
PRE = Pre-vaccination at Day 0, POST = Post-vaccination at 28 days after the last vaccination

Table 92: Mean Geometric Increase (MGI) for HI antibody titers at day 28 or day 56 by age strata (ATP cohort)

				MGI		
					95% CI	
Strain	Group	Sub-group	N	Value	LL	UL
A/California/7/2009 (H1N1) (1/DIL)	D-QIV	3 - 8 years	488	17.2	15.6	19.0
		9 - 17 years	302	19.2	16.7	22.2
	FLUARIX	3 - 8 years	510	17.2	15.6	18.9
		9 - 17 years	308	17.7	15.2	20.5
	TIV-2	3 - 8 years	503	17.2	15.6	18.9
		9 - 17 years	297	23.3	20.3	26.9
	D-QIV-Y	6 - 17 months	70	8.2	6.4	10.6
		18 - 35 months	162	13.7	11.7	16.0
A/Victoria/210/2009 (H3N2) (1/DIL)	D-QIV	3 - 8 years	488	8.4	7.6	9.3
		9 - 17 years	302	7.2	6.2	8.2
	FLUARIX	3 - 8 years	510	7.3	6.6	8.1
		9 - 17 years	308	7.1	6.2	8.1
	TIV-2	3 - 8 years	503	7.8	7.1	8.5
		9 - 17 years	297	7.1	6.2	8.1
	D-QIV-Y	6 - 17 months	70	7.3	5.9	9.0
		18 - 35 months	162	12.1	10.2	14.3
B/Brisbane/60/2008 (Victoria) (1/DIL)	D-QIV	3 - 8 years	488	8.8	7.9	9.8
		9 - 17 years	302	6.7	5.8	7.8
	FLUARIX	3 - 8 years	510	8.8	7.9	9.8
		9 - 17 years	308	6.6	5.7	7.6
	TIV-2	3 - 8 years	503	2.8	2.6	3.1
		9 - 17 years	297	2.4	2.1	2.7
	D-QIV-Y	6 - 17 months	70	6.9	5.4	8.9
		18 - 35 months	162	11.3	9.6	13.2
B/Brisbane/3/2007 (Yamagata) (1/DIL)	D-QIV	3 - 8 years	488	8.8	7.9	9.8
		9 - 17 years	302	5.6	4.9	6.3
	FLUARIX	3 - 8 years	510	3.1	2.9	3.4
		9 - 17 years	308	2.5	2.3	2.8
	TIV-2	3 - 8 years	503	9.9	8.9	11.0
		9 - 17 years	297	4.9	4.3	5.6
	D-QIV-Y	6 - 17 months	70	9.5	7.0	12.8
		18 - 35 months	162	14.8	12.2	18.0

D-QIV = Subjects of 3-17 years received D-QIV

FLUARIX = Subjects of 3-17 years received TIV-1 (*Fluarix*) TIV-2 = Subjects of 3-17 years received TIV-2

D-QIV-Y = Subjects of 6-35 months received D-QIV

N = Number of subjects with pre- and post-vaccination results available

MGI = Mean Geometric increase in serum HI GMTs post-vaccination

Reviewer's comment
The descriptive analyses shows the seroconversion and seroprotection rates of D-QIV, TIV-1 and TIV-2 are similar for the age groups 3-8 years of age and 9-17 years of age for all four strains.
However in the D-QIV-Y group both the seroconversion and seroprotection rates are lower in the age group 6 -17 months compared to the group 18-35 months for all strains.

Seroconversion rates:

- ***61.4%** in the 6-17 month age group versus **85.2%** in the 18-35 month age group for the A/California/7/2009 (H1N1) strain.*
- ***52.9%** in the 6-17 month age group versus **75.3%** in the 18-35 month age group for the A/Victoria/210/2009 (H3N2) strain.*
- ***51.4%** in the 6-17 month age group versus **75.3%** in the 18-35 month age group for the B/Brisbane/60/2008 (Victoria) strain.*
- ***74.3%** in the 6-17 month age group versus **85.8%** in the 18-35 month age group for the B/Brisbane/3/2007 (Yamagata) strain*

Seroprotection rates (SPRs)
The comparison of the post-vaccination SPR between the two age groups is:

- ***63.4%** in the 6-17 month age group versus **87.1%** in the 18-35 month age group for the A/California/7/2009 (H1N1) strain.*
- ***54.9%** in the 6-17 month age group versus **79.8%** in the 18-35 month age group for the A/Victoria/210/2009 (H3N2) strain.*
- ***53.5%** in the 6-17 month age group versus **79.1%** in the 18-35 month age group for the B/Brisbane/60/2008 (Victoria) strain.*
- ***85.9%** in the 6-17 month age group versus **92.6%** in the 18-35 month age group for the B/Brisbane/3/2007 (Yamagata) strain.*

Note: All subgroup analyses are descriptive. No inferential analysis has conducted to show if the difference are statistically significant.

Analysis by Gender

Seropositivity rates and GMTs, SCRs, SPRs and MGIs analyzed by gender are presented in table 93 to table 96.

The results in these tables show similar seropositivity, SCR and SPR rates as well as GMT and MGI values in males and females.

Table 93: Seropositivity rates and GMTs for HI antibody titers at day 0 and day 28 or day 56 by gender (ATP cohort)

					≥ 10 1/DIL				GMT		
							95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL
A/California/7/2009 (H1N1)	D-QIV	MALE	PRE	396	268	67.7	62.8	72.3	23.0	20.2	26.1
			POST	397	396	99.7	98.6	100	397.7	356.7	443.3
		FEMALE	PRE	394	243	61.7	56.7	66.5	20.3	17.9	23.1
			POST	394	394	100	99.1	100	374.9	335.3	419.2
	FLUARIX	MALE	PRE	427	300	70.3	65.7	74.6	23.5	20.9	26.4
			POST	426	422	99.1	97.6	99.7	445.2	400.1	495.4
		FEMALE	PRE	392	264	67.3	62.5	72.0	26.5	23.1	30.5
			POST	392	391	99.7	98.6	100	420.5	375.8	470.6
	TIV-2	MALE	PRE	418	267	63.9	59.1	68.5	21.6	19.0	24.6
			POST	419	416	99.3	97.9	99.9	409.1	365.9	457.3
		FEMALE	PRE	382	241	63.1	58.0	67.9	22.6	19.7	25.8
			POST	382	382	100	99.0	100	437.2	391.9	487.7
	D-QIV-Y	MALE	PRE	136	48	35.3	27.3	43.9	14.3	11.1	18.5
			POST	137	132	96.4	91.7	98.8	141.6	105.5	190.1
		FEMALE	PRE	96	24	25.0	16.7	34.9	9.9	7.6	12.9
			POST	97	95	97.9	92.7	99.7	137.7	103.6	183.1
A/Victoria/210/2009 (H3N2)	D-QIV	MALE	PRE	396	324	81.8	77.7	85.5	30.0	26.6	33.9
			POST	397	397	100	99.1	100	229.4	210.3	250.4
		FEMALE	PRE	394	305	77.4	73.0	81.4	28.0	24.7	31.7
			POST	394	393	99.7	98.6	100	228.1	208.7	249.3
	FLUARIX	MALE	PRE	427	357	83.6	79.7	87.0	31.7	28.2	35.6
			POST	426	424	99.5	98.3	99.9	224.4	205.2	245.5
		FEMALE	PRE	392	316	80.6	76.3	84.4	31.1	27.4	35.3
			POST	392	392	100	99.1	100	230.5	210.5	252.5
	TIV-2	MALE	PRE	418	326	78.0	73.7	81.9	30.2	26.7	34.3
			POST	419	418	99.8	98.7	100	225.9	206.0	247.7
		FEMALE	PRE	382	307	80.4	76.0	84.2	32.4	28.4	36.8
			POST	382	382	100	99.0	100	243.3	221.5	267.2
	D-QIV-Y	MALE	PRE	136	27	19.9	13.5	27.6	8.0	6.7	9.6
			POST	137	136	99.3	96.0	100	81.6	65.8	101.2
		FEMALE	PRE	96	24	25.0	16.7	34.9	9.4	7.4	12.1
			POST	97	96	99.0	94.4	100	96.5	73.2	127.4
B/Brisbane/60/2008 (Victoria)	D-QIV	MALE	PRE	396	306	77.3	72.8	81.3	27.9	24.6	31.7
			POST	397	397	100	99.1	100	218.7	197.9	241.7
		FEMALE	PRE	394	313	79.4	75.1	83.3	34.2	29.9	39.1
			POST	394	394	100	99.1	100	272.9	247.0	301.5
	FLUARIX	MALE	PRE	427	340	79.6	75.5	83.3	30.2	26.6	34.3
			POST	426	425	99.8	98.7	100	255.4	231.9	281.3
		FEMALE	PRE	392	299	76.3	71.7	80.4	31.9	27.8	36.6
			POST	392	391	99.7	98.6	100	235.4	213.2	260.0

					≥ 10 1/DIL				GMT		
							95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL
	TIV-2	MALE	PRE	418	323	77.3	73.0	81.2	29.0	25.5	32.9
			POST	419	411	98.1	96.3	99.2	81.0	72.7	90.3
		FEMALE	PRE	382	305	79.8	75.5	83.8	38.6	33.4	44.6
			POST	382	373	97.6	95.6	98.9	97.2	86.2	109.6
	D-QIV-Y	MALE	PRE	136	44	32.4	24.6	40.9	9.3	7.8	11.2
			POST	137	131	95.6	90.7	98.4	88.2	68.9	112.9
		FEMALE	PRE	96	27	28.1	19.4	38.2	8.6	6.9	10.7
			POST	97	96	99.0	94.4	100	84.1	66.1	106.9

D-QIV=Subjects of 3-17 years received D-QIV
FLUARIX = Subjects of 3-17 years received TIV-1 (*Fluarix*)
TIV-2 = Subjects of 3-17 years received TIV-2
D-QIV-Y = Subjects of 6-35 months received D-QIV
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titer within the specified range
PRE = Pre-vaccination at Day 0, POST = Post-vaccination at 28 days after the last vaccination

Table 94: Seroconversion rate (SCR) for HI antibody titers at day 28 or 56 by gender (ATP cohort)

				SCR			
						95% CI	
Strain	Group	Sub-group	N	n	%	LL	UL
A/California/7/2009 (H1N1)	D-QIV	MALE	396	359	90.7	87.4	93.3
		FEMALE	394	363	92.1	89.0	94.6
	FLUARIX	MALE	426	390	91.5	88.5	94.0
		FEMALE	392	345	88.0	84.4	91.1
	TIV-2	MALE	418	385	92.1	89.1	94.5
		FEMALE	382	348	91.1	87.8	93.8
	D-QIV-Y	MALE	136	99	72.8	64.5	80.1
		FEMALE	96	82	85.4	76.7	91.8
A/Victoria/210/2009 (H3N2)	D-QIV	MALE	396	284	71.7	67.0	76.1
		FEMALE	394	287	72.8	68.2	77.2
	FLUARIX	MALE	426	310	72.8	68.3	76.9
		FEMALE	392	268	68.4	63.5	72.9
	TIV-2	MALE	418	300	71.8	67.2	76.0
		FEMALE	382	275	72.0	67.2	76.4
	D-QIV-Y	MALE	136	91	66.9	58.3	74.7
		FEMALE	96	68	70.8	60.7	79.7
B/Brisbane/60/2008 (Victoria)	D-QIV	MALE	396	279	70.5	65.7	74.9
		FEMALE	394	274	69.5	64.7	74.1
	FLUARIX	MALE	426	298	70.0	65.4	74.3
		FEMALE	392	262	66.8	61.9	71.5
	TIV-2	MALE	418	127	30.4	26.0	35.0
		FEMALE	382	110	28.8	24.3	33.6
	D-QIV-Y	MALE	136	88	64.7	56.1	72.7
		FEMALE	96	70	72.9	62.9	81.5
B/Brisbane/3/2007 (Yamagata)	D-QIV	MALE	396	274	69.2	64.4	73.7
		FEMALE	394	299	75.9	71.4	80.0
	FLUARIX	MALE	426	167	39.2	34.5	44.0
		FEMALE	392	136	34.7	30.0	39.6
	TIV-2	MALE	418	303	72.5	67.9	76.7

				SCR			
						95% CI	
Strain	Group	Sub-group	N	n	%	LL	UL
		FEMALE	382	263	68.8	63.9	73.5
	D-QIV-Y	MALE	136	110	80.9	73.3	87.1
		FEMALE	96	81	84.4	75.5	91.0

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received TIV-1 (*Fluarix*) TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV

Seroconversion defined as:

- For initially seronegative subjects, antibody titer ≥ 40 1/DIL after vaccination
- For initially seropositive subjects, antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer

N = Number of subjects with pre- and post-vaccination results available

n/% = Number/percentage of seroconverted subjects

Table 95: Seroprotection rates (SPR HI titer ≥ 40) for HI antibody titers at day 0 and day 28 or 56 by gender (ATP cohort)

					SPR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
A/California/7/2009 (H1N1)	D-QIV	MALE	PRE	396	176	44.4	39.5	49.5
			POST	397	384	96.7	94.5	98.2
		FEMALE	PRE	394	167	42.4	37.5	47.4
			POST	394	380	96.4	94.1	98.0
	FLUARIX	MALE	PRE	427	201	47.1	42.3	51.9
			POST	426	414	97.2	95.1	98.5
		FEMALE	PRE	392	203	51.8	46.7	56.8
			POST	392	379	96.7	94.4	98.2
	TIV-2	MALE	PRE	418	176	42.1	37.3	47.0
			POST	419	406	96.9	94.8	98.3
		FEMALE	PRE	382	177	46.3	41.2	51.5
			POST	382	372	97.4	95.2	98.7
	D-QIV-Y	MALE	PRE	136	42	30.9	23.2	39.4
			POST	137	104	75.9	67.9	82.8
		FEMALE	PRE	96	18	18.8	11.5	28.0
			POST	97	83	85.6	77.0	91.9
A/Victoria/210/2009 (H3N2)	D-QIV	MALE	PRE	396	197	49.7	44.7	54.8
			POST	397	390	98.2	96.4	99.3
		FEMALE	PRE	394	184	46.7	41.7	51.8
			POST	394	385	97.7	95.7	99.0
	FLUARIX	MALE	PRE	427	216	50.6	45.7	55.4
			POST	426	415	97.4	95.4	98.7
		FEMALE	PRE	392	196	50.0	44.9	55.1
			POST	392	385	98.2	96.4	99.3
	TIV-2	MALE	PRE	418	210	50.2	45.3	55.1
			POST	419	404	96.4	94.2	98.0
		FEMALE	PRE	382	199	52.1	47.0	57.2
			POST	382	369	96.6	94.3	98.2
	D-QIV-Y	MALE	PRE	136	18	13.2	8.0	20.1
			POST	137	97	70.8	62.4	78.3
		FEMALE	PRE	96	16	16.7	9.8	25.6
			POST	97	72	74.2	64.3	82.6
B/Brisbane/60/2008 (Victoria)	D-QIV	MALE	PRE	396	183	46.2	41.2	51.3

					SPR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
			POST	397	388	97.7	95.7	99.0
		FEMALE	PRE	394	198	50.3	45.2	55.3
			POST	394	382	97.0	94.7	98.4
	FLUARIX	MALE	PRE	427	205	48.0	43.2	52.9
			POST	426	411	96.5	94.3	98.0
		FEMALE	PRE	392	191	48.7	43.7	53.8
			POST	392	379	96.7	94.4	98.2
	TIV-2	MALE	PRE	418	194	46.4	41.6	51.3
			POST	419	326	77.8	73.5	81.7
		FEMALE	PRE	382	205	53.7	48.5	58.8
			POST	382	313	81.9	77.7	85.7
	D-QIV-Y	MALE	PRE	136	18	13.2	8.0	20.1
			POST	137	93	67.9	59.4	75.6
		FEMALE	PRE	96	10	10.4	5.1	18.3
			POST	97	74	76.3	66.6	84.3

Table 96: Mean Geometric Increase (MGI) for HI antibody titers at day 28 or day 56 by gender (ATP cohort)

				MGI		
					95% CI	
Strain	Group	Sub-group	N	Value	LL	UL
A/California/7/2009 (H1N1) (1/DIL)	D-QIV	MALE	396	17.5	15.5	19.8
		FEMALE	394	18.4	16.5	20.6
	FLUARIX	MALE	426	18.9	16.8	21.1
		FEMALE	392	15.8	14.1	17.8
	TIV-2	MALE	418	19.1	17.1	21.3
		FEMALE	382	19.4	17.2	21.8
	D-QIV-Y	MALE	136	10.1	8.5	12.1
		FEMALE	96	14.4	11.8	17.7
A/Victoria/210/2009 (H3N2) (1/DIL)	D-QIV	MALE	396	7.6	6.8	8.6
		FEMALE	394	8.2	7.3	9.1
	FLUARIX	MALE	426	7.1	6.4	7.8
		FEMALE	392	7.4	6.6	8.4
	TIV-2	MALE	418	7.5	6.7	8.3
		FEMALE	382	7.5	6.7	8.5
	D-QIV-Y	MALE	136	10.2	8.4	12.4
		FEMALE	96	10.5	8.6	12.9
B/Brisbane/60/2008 (Victoria) (1/DIL)	D-QIV	MALE	396	7.9	7.0	8.9
		FEMALE	394	8.0	7.0	9.0
	FLUARIX	MALE	426	8.4	7.5	9.5
		FEMALE	392	7.4	6.5	8.4
	TIV-2	MALE	418	2.8	2.5	3.1
		FEMALE	382	2.5	2.3	2.8
	D-QIV-Y	MALE	136	9.6	7.9	11.7
		FEMALE	96	10.0	8.4	11.9
B/Brisbane/3/2007 (Yamagata) (1/DIL)	D-QIV	MALE	396	7.1	6.3	8.0
		FEMALE	394	7.7	6.9	8.7
	FLUARIX	MALE	426	3.0	2.8	3.3
		FEMALE	392	2.8	2.5	3.1
	TIV-2	MALE	418	7.7	6.9	8.7

				MGI		
					95% CI	
Strain	Group	Sub-group	N	Value	LL	UL
		FEMALE	382	7.5	6.6	8.5
	D-QIV-Y	MALE	136	12.8	10.2	16.1
		FEMALE	96	13.2	10.4	16.6

D-QIV = Subjects of 3-17 years received D-QIV
FLUARIX = Subjects of 3-17 years received TIV-1 (*Fluarix*)
TIV-2 = Subjects of 3-17 years received TIV-2
D-QIV-Y = Subjects of 6-35 months received D-QIV
N = Number of subjects with pre- and post-vaccination results available
MGI = Mean Geometric increase in serum HI GMTs post-vaccination

Analysis by Race

Results of descriptive analysis by race (white/Caucasian versus non-white/Caucasian) are presented in tables 96 to table 98 for the immunogenicity endpoints.

Table 96: Seroconversion rate (SCR) for HI antibodies against each strain at day 28 or 56 by race (ATP cohort)

				SCR			
						95% CI	
Strain	Group	Sub-group	N	n	%	LL	UL
Flu A/CAL/7/09 (H1N1).HA Ab	D-QIV	White/Caucasian	446	406	91.0	88.0	93.5
		Non-White/Caucasian	344	316	91.9	88.5	94.5
	FLUARIX	White/Caucasian	451	397	88.0	84.7	90.9
		Non-White/Caucasian	367	338	92.1	88.8	94.6
	TIV-2	White/Caucasian	444	403	90.8	87.7	93.3
		Non-White/Caucasian	356	330	92.7	89.5	95.2
	D-QIV-Y	White/Caucasian	168	132	78.6	71.6	84.5
		Non-White/Caucasian	64	49	76.6	64.3	86.2
Flu A/Victoria/210/09 (H3N2).HA Ab	D-QIV	White/Caucasian	446	323	72.4	68.0	76.5
		Non-White/Caucasian	344	248	72.1	67.0	76.8
	FLUARIX	White/Caucasian	451	328	72.7	68.4	76.8
		Non-White/Caucasian	367	250	68.1	63.1	72.9
	TIV-2	White/Caucasian	444	326	73.4	69.1	77.5
		Non-White/Caucasian	356	249	69.9	64.9	74.7
	D-QIV-Y	White/Caucasian	168	112	66.7	59.0	73.7
		Non-White/Caucasian	64	47	73.4	60.9	83.7
Flu B/Bri/60/08 (Victoria).HA Ab	D-QIV	White/Caucasian	446	299	67.0	62.5	71.4
		Non-White/Caucasian	344	254	73.8	68.9	78.4
	FLUARIX	White/Caucasian	451	308	68.3	63.8	72.6
		Non-White/Caucasian	367	252	68.7	63.6	73.4
	TIV-2	White/Caucasian	444	123	27.7	23.6	32.1
		Non-White/Caucasian	356	114	32.0	27.2	37.1
	D-QIV-Y	White/Caucasian	168	108	64.3	56.5	71.5
		Non-White/Caucasian	64	50	78.1	66.0	87.5
Flu B/Bri/3/07 (Yamagata).HA Ab	D-QIV	White/Caucasian	446	312	70.0	65.5	74.2
		Non-White/Caucasian	344	261	75.9	71.0	80.3

				SCR			
						95% CI	
Strain	Group	Sub-group	N	n	%	LL	UL
	FLUARIX	White/Caucasian	451	169	37.5	33.0	42.1
		Non-White/Caucasian	367	134	36.5	31.6	41.7
	TIV-2	White/Caucasian	444	309	69.6	65.1	73.8
		Non-White/Caucasian	356	257	72.2	67.2	76.8
	D-QIV-Y	White/Caucasian	168	135	80.4	73.5	86.1
		Non-White/Caucasian	64	56	87.5	76.8	94.4

D-QIV = Subjects of 3-17 years received D-QIV

FLUARIX = Subjects of 3-17 years received Fluarix

TIV-2 = Subjects of 3-17 years received TIV-2

D-QIV-Y = Subjects of 6-35 months received D-QIV

Seroconversion defined as:

For initially seronegative subjects, antibody titer ≥ 40 1/DIL after vaccination

For initially seropositive subjects, antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer

N = Number of subjects with pre- and post-vaccination results available

n/% = Number/percentage of seroconverted subjects

The SCR are similar in both White/Caucasian and Non-white/Caucasian subjects.

Table 97: Seroprotection rates (SPR) for HI antibodies against each strain at day 0 and day 28 or 56 by race (ATP cohort).

					SPR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
A/CAL/7/09 (H1N1)	D-QIV	White/Caucasian	PRE	446	199	44.6	39.9	49.4
			POST	447	432	96.6	94.5	98.1
		Non-White/Caucasian	PRE	344	144	41.9	36.6	47.3
			POST	344	332	96.5	94	98.2
	FLUARIX	White/Caucasian	PRE	452	231	51.1	46.4	55.8
			POST	451	434	96.2	94	97.8
		Non-White/Caucasian	PRE	367	173	47.1	41.9	52.4
			POST	367	359	97.8	95.8	99.1
	TIV-2	White/Caucasian	PRE	444	194	43.7	39	48.4
			POST	445	426	95.7	93.4	97.4
		Non-White/Caucasian	PRE	356	159	44.7	39.4	50
			POST	356	352	98.9	97.1	99.7
	D-QIV-Y	White/Caucasian	PRE	168	35	20.8	15	27.8
			POST	170	135	79.4	72.5	85.2
		Non-White/Caucasian	PRE	64	25	39.1	27.1	52.1
			POST	64	52	81.3	69.5	89.9
A/Victoria/210/09 (H3N2	D-QIV	White/Caucasian	PRE	446	197	44.2	39.5	48.9
			POST	447	436	97.5	95.6	98.8
		Non-White/Caucasian	PRE	344	184	53.5	48.1	58.9
			POST	344	339	98.5	96.6	99.5
	FLUARIX	White/Caucasian	PRE	452	208	46	41.4	50.7
			POST	451	439	97.3	95.4	98.6
		Non-White/Caucasian	PRE	367	204	55.6	50.3	60.7
			POST	367	361	98.4	96.5	99.4
	TIV-2	White/Caucasian	PRE	444	187	42.1	37.5	46.9
			POST	445	422	94.8	92.3	96.7
		Non-White/Caucasian	PRE	356	222	62.4	57.1	67.4

			POST	356	351	98.6	96.8	99.5
	D-QIV-Y	White/Caucasian	PRE	168	16	9.5	5.5	15
			POST	170	117	68.8	61.3	75.7
		Non-White/Caucasian	PRE	64	18	28.1	17.6	40.8
			POST	64	52	81.3	69.5	89.9
B/Bri/60/08 (Victoria)	D-QIV	White/Caucasian	PRE	446	204	45.7	41	50.5
			POST	447	430	96.2	94	97.8
		Non-White/Caucasian	PRE	344	177	51.5	46	56.8
			POST	344	340	98.8	97	99.7
	FLUARIX	White/Caucasian	PRE	452	202	44.7	40	49.4
			POST	451	433	96	93.8	97.6
		Non-White/Caucasian	PRE	367	194	52.9	47.6	58.1
			POST	367	357	97.3	95	98.7
	TIV-2	White/Caucasian	PRE	444	210	47.3	42.6	52.1
			POST	445	337	75.7	71.5	79.6
		Non-White/Caucasian	PRE	356	189	53.1	47.8	58.4
			POST	356	302	84.8	80.7	88.4
	D-QIV-Y	White/Caucasian	PRE	168	13	7.7	4.2	12.9
			POST	170	113	66.5	58.8	73.5
		Non-White/Caucasian	PRE	64	15	23.4	13.8	35.7
			POST	64	54	84.4	73.1	92.2
B/Bri/3/07 (Yamagata)	D-QIV	White/Caucasian	PRE	446	299	67	62.5	71.4
			POST	447	443	99.1	97.7	99.8
		Non-White/Caucasian	PRE	344	266	77.3	72.5	81.6
			POST	344	342	99.4	97.9	99.9
	FLUARIX	White/Caucasian	PRE	452	301	66.6	62	70.9
			POST	451	419	92.9	90.1	95.1
		Non-White/Caucasian	PRE	367	274	74.7	69.9	79
			POST	367	353	96.2	93.7	97.9
	TIV-2	White/Caucasian	PRE	444	296	66.7	62.1	71
			POST	445	442	99.3	98	99.9
		Non-White/Caucasian	PRE	356	297	83.4	79.1	87.1
			POST	356	356	100	99	100
	D-QIV-Y	White/Caucasian	PRE	168	26	15.5	10.4	21.8
			POST	170	153	90	84.5	94.1
		Non-White/Caucasian	PRE	64	22	34.4	22.9	47.3
			POST	64	59	92.2	82.7	97.4

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received Fluarix,
TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV
N = Number of subjects with available results
n/% = Number/percentage of seroprotected subjects (HI titer ≥ 40 1/DIL)
PRE = Pre-vaccination at Day 0, POST= Post-vaccination at 28 days after the last vaccination

Table 98: Mean geometric increase (MGI) for HI antibodies against each strain at day 28 or day 56 by race (ATP cohort)

				MGI		
					95% CI	
Strain	Group	Sub-group	N	Value	LL	UL
Flu A/CAL/7/09 (H1N1).HA Ab (1/DIL)	D-QIV	White/Caucasian	446	17.0	15.1	19.0
		Non-White/Caucasian	344	19.4	17.2	21.8
	FLUARIX	White/Caucasian	451	15.8	14.2	17.7
		Non-White/Caucasian	367	19.4	17.2	21.9
	TIV-2	White/Caucasian	444	18.0	16.2	20.1
		Non-White/Caucasian	356	20.9	18.5	23.6
	D-QIV-Y	White/Caucasian	168	12.2	10.4	14.3
		Non-White/Caucasian	64	10.6	8.2	13.7
Flu A/Victoria/210/09 (H3N2).HA Ab (1/DIL)	D-QIV	White/Caucasian	446	8.1	7.2	9.0
		Non-White/Caucasian	344	7.7	6.8	8.7
	FLUARIX	White/Caucasian	451	7.6	6.8	8.5
		Non-White/Caucasian	367	6.7	6.0	7.6
	TIV-2	White/Caucasian	444	8.3	7.4	9.2

				MGI		
					95% CI	
Strain	Group	Sub-group	N	Value	LL	UL
		Non-White/Caucasian	356	6.6	5.9	7.4
	D-QIV-Y	White/Caucasian	168	10.3	8.8	12.1
		Non-White/Caucasian	64	10.4	7.9	13.8
Flu B/Bri/60/08 (Victoria).HA Ab (1/DIL)	D-QIV	White/Caucasian	446	7.6	6.7	8.5
		Non-White/Caucasian	344	8.4	7.4	9.6
	FLUARIX	White/Caucasian	451	8.1	7.2	9.2
		Non-White/Caucasian	367	7.6	6.7	8.7
	TIV-2	White/Caucasian	444	2.8	2.5	3.0
		Non-White/Caucasian	356	2.5	2.3	2.8
	D-QIV-Y	White/Caucasian	168	9.5	8.1	11.2
		Non-White/Caucasian	64	10.3	7.8	13.7
Flu B/Bri/3/07 (Yamagata).HA Ab (1/DIL)	D-QIV	White/Caucasian	446	6.9	6.1	7.7
		Non-White/Caucasian	344	8.2	7.2	9.2
	FLUARIX	White/Caucasian	451	2.9	2.7	3.2
		Non-White/Caucasian	367	2.9	2.6	3.2
	TIV-2	White/Caucasian	444	7.6	6.7	8.5
		Non-White/Caucasian	356	7.7	6.8	8.7
	D-QIV-Y	White/Caucasian	168	12.6	10.4	15.1
		Non-White/Caucasian	64	14.0	9.8	19.9

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received Fluarix,
TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV
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 titer to the Day 0 reciprocal HI titer

Reviewer's comment:
The immunogenicity endpoints SPR, SCR, GMT and MGI all have similar results in both White/Caucasian and Non-white/Caucasian subjects.

Analysis by Region
Immunogenicity results by region are provided in following tables (tables 99 to 101)

Table 99: Seroconversion rate (SCR) for HI antibodies against each strain at day 28 or 56 by region (ATP cohort)

				SCR			
						95% CI	
Strain	Group	Sub-group	N	n	%	LL	UL
A/California/7/2009 (H1N1)	D-QIV	US	323	282	87.3	83.2	90.7
		Europe	267	251	94.0	90.5	96.5
		Asia	200	189	94.5	90.4	97.2
	FLUARIX	US	328	283	86.3	82.1	89.8
		Europe	278	252	90.6	86.6	93.8
		Asia	212	200	94.3	90.3	97.0
	TIV-2	US	324	286	88.3	84.3	91.6
		Europe	270	251	93.0	89.2	95.7
		Asia	206	196	95.1	91.3	97.6
	D-QIV-Y	Europe	197	153	77.7	71.2	83.3
		Asia	35	28	80.0	63.1	91.6
A/Victoria/210/2009 (H3N2)	D-QIV	US	323	232	71.8	66.6	76.7
		Europe	267	198	74.2	68.5	79.3
		Asia	200	141	70.5	63.7	76.7
	FLUARIX	US	328	218	66.5	61.1	71.6

				SCR			
						95% CI	
Strain	Group	Sub-group	N	n	%	LL	UL
		Europe	278	211	75.9	70.4	80.8
		Asia	212	149	70.3	63.6	76.3
	TIV-2	US	324	228	70.4	65.1	75.3
		Europe	270	202	74.8	69.2	79.9
		Asia	206	145	70.4	63.6	76.5
	D-QIV-Y	Europe	197	131	66.5	59.4	73.0
		Asia	35	28	80.0	63.1	91.6
B/Brisbane/60/2008 (Victoria)	D-QIV	US	323	216	66.9	61.4	72.0
		Europe	267	186	69.7	63.8	75.1
		Asia	200	151	75.5	68.9	81.3
	FLUARIX	US	328	195	59.5	53.9	64.8
		Europe	278	209	75.2	69.7	80.1
		Asia	212	156	73.6	67.1	79.4
	TIV-2	US	324	77	23.8	19.2	28.8
		Europe	270	85	31.5	26.0	37.4
		Asia	206	75	36.4	29.8	43.4
	D-QIV-Y	Europe	197	130	66.0	58.9	72.6
		Asia	35	28	80.0	63.1	91.6
B/Brisbane/3/2007 (Yamagata)	D-QIV	US	323	233	72.1	66.9	77.0
		Europe	267	186	69.7	63.8	75.1
		Asia	200	154	77.0	70.5	82.6
	FLUARIX	US	328	114	34.8	29.6	40.2
		Europe	278	112	40.3	34.5	46.3
		Asia	212	77	36.3	29.8	43.2
	TIV-2	US	324	205	63.3	57.8	68.5
		Europe	270	204	75.6	70.0	80.6
		Asia	206	157	76.2	69.8	81.9
	D-QIV-Y	Europe	197	159	80.7	74.5	86.0
		Asia	35	32	91.4	76.9	98.2

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received Fluarix
TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV
US=Subjects from the United States, Europe = Subjects from Germany, France and Czech Republic, Asia = Subjects from Philippines
Seroconversion defined as:

- For initially seronegative subjects, antibody titer ≥ 40 1/DIL after vaccination
- For initially seropositive subjects, antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer

N = Number of subjects with pre- and post-vaccination results available
n/% = Number/percentage of seroconverted subjects

Table 100: Seroprotection rates (SPR) for HI antibodies against each strain at day 0 and day 28 or 56 by region (ATP cohort)

					SPR			
							95% CI	
Strain	Group	Sub-	Timing	N	n	%	LL	UL
A/California/7/2009 (H1N1)	D-QIV	US	PRE	323	159	49.2	43.6	54.8
			POST	323	308	95.4	92.5	97.4
		Europe	PRE	267	116	43.4	37.4	49.6
			POST	268	259	96.6	93.7	98.5
		Asia	PRE	200	68	34	27.5	41
			POST	200	197	98.5	95.7	99.7
	FLUARIX	US	PRE	328	176	53.7	48.1	59.2
			POST	328	312	95.1	92.2	97.2
		Europe	PRE	279	139	49.8	43.8	55.8
			POST	278	271	97.5	94.9	99

					SPR			
							95% CI	
Strain	Group	Sub-	Timing	N	n	%	LL	UL
		Asia	PRE	212	89	42	35.3	48.9
			POST	212	210	99.1	96.6	99.9
	TIV-2	US	PRE	324	166	51.2	45.6	56.8
			POST	324	313	96.6	94	98.3
		Europe	PRE	270	108	40	34.1	46.1
			POST	271	260	95.9	92.9	98
		Asia	PRE	206	79	38.3	31.7	45.4
			POST	206	205	99.5	97.3	100
	D-QIV-Y	Europe	PRE	197	43	21.8	16.3	28.3
			POST	199	157	78.9	72.6	84.3
		Asia	PRE	35	17	48.6	31.4	66
			POST	35	30	85.7	69.7	95.2
A/Victoria/210/2009 (H3N2)	D-QIV	US	PRE	323	129	39.9	34.6	45.5
			POST	323	314	97.2	94.8	98.7
		Europe	PRE	267	130	48.7	42.6	54.9
			POST	268	261	97.4	94.7	98.9
		Asia	PRE	200	122	61	53.9	67.8
			POST	200	200	100	98.2	100
	FLUARIX	US	PRE	328	159	48.5	42.9	54
			POST	328	320	97.6	95.3	98.9
		Europe	PRE	279	120	43	37.1	49
			POST	278	268	96.4	93.5	98.3
		Asia	PRE	212	133	62.7	55.8	69.3
			POST	212	212	100	98.3	100
	TIV-2	US	PRE	324	142	43.8	38.3	49.4
			POST	324	309	95.4	92.5	97.4
		Europe	PRE	270	121	44.8	38.8	51
			POST	271	259	95.6	92.4	97.7
		Asia	PRE	206	146	70.9	64.2	77
			POST	206	205	99.5	97.3	100
	D-QIV-Y	Europe	PRE	197	19	9.6	5.9	14.7
			POST	199	137	68.8	61.9	75.2
		Asia	PRE	35	15	42.9	26.3	60.6
			POST	35	32	91.4	76.9	98.2
B/Brisbane/60/2008 (Victoria)	D-QIV	US	PRE	323	174	53.9	48.3	59.4
			POST	323	317	98.1	96	99.3
		Europe	PRE	267	111	41.6	35.6	47.7
			POST	268	257	95.9	92.8	97.9
		Asia	PRE	200	96	48	40.9	55.2
			POST	200	196	98	95	99.5
	FLUARIX	US	PRE	328	175	53.4	47.8	58.9
			POST	328	313	95.4	92.6	97.4
		Europe	PRE	279	109	39.1	33.3	45.1
			POST	278	269	96.8	93.9	98.5
		Asia	PRE	212	112	52.8	45.9	59.7
			POST	212	208	98.1	95.2	99.5
	TIV-2	US	PRE	324	182	56.2	50.6	61.7
			POST	324	262	80.9	76.2	85
		Europe	PRE	270	107	39.6	33.8	45.7

					SPR			
							95% CI	
Strain	Group	Sub-	Timing	N	n	%	LL	UL
			POST	271	197	72.7	67	77.9
		Asia	PRE	206	110	53.4	46.3	60.4
			POST	206	180	87.4	82.1	91.6
	D-QIV-Y	Europe	PRE	197	17	8.6	5.1	13.5
			POST	199	137	68.8	61.9	75.2
		Asia	PRE	35	11	31.4	16.9	49.3
			POST	35	30	85.7	69.7	95.2
B/Brisbane/3/2007 (Yamagata)	D-QIV	US	PRE	323	236	73.1	67.9	77.8
			POST	323	320	99.1	97.3	99.8
		Europe	PRE	267	176	65.9	59.9	71.6
			POST	268	266	99.3	97.3	99.9
		Asia	PRE	200	153	76.5	70	82.2
			POST	200	199	99.5	97.2	100
	FLUARIX	US	PRE	328	231	70.4	65.2	75.3
			POST	328	310	94.5	91.5	96.7
		Europe	PRE	279	178	63.8	57.9	69.4
			POST	278	255	91.7	87.8	94.7
		Asia	PRE	212	166	78.3	72.1	83.7
			POST	212	207	97.6	94.6	99.2
	TIV-2	US	PRE	324	252	77.8	72.9	82.2
			POST	324	323	99.7	98.3	100
		Europe	PRE	270	164	60.7	54.6	66.6
			POST	271	269	99.3	97.4	99.9
		Asia	PRE	206	177	85.9	80.4	90.4
			POST	206	206	100	98.2	100
	D-QIV-Y	Europe	PRE	197	30	15.2	10.5	21
			POST	199	178	89.4	84.3	93.3
		Asia	PRE	35	18	51.4	34	68.6
			POST	35	34	97.1	85.1	99.9

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received Fluarix
TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV
US=Subjects from the United States, Europe = Subjects from Germany, France and Czech Republic, Asia = Subjects from Philippines
N = Number of subjects with available results
n/% = Number/percentage of seroprotected subjects (HI titer ≥ 40 1/DIL)
PRE = Pre-vaccination at Day 0
POST = Post-vaccination at 28 days after the last vaccination

Table 101: Mean Geometric Increase (MGI) for HI antibodies against each strain at day 28 or day 56 by region (ATP cohort)

				MGI		
					95% CI	
Strain	Group	Sub-group	N	Value	LL	UL
A/California/7/2009 (H1N1) (1/DIL)	D-QIV	US	323	15.3	13.3	17.6
		Europe	267	18.2	16.0	20.6
		Asia	200	23.1	19.9	26.7
	FLUARIX	US	328	14.3	12.5	16.3
		Europe	278	17.2	14.9	19.8
		Asia	212	23.7	20.4	27.5
	TIV-2	US	324	16.1	14.1	18.4
		Europe	270	19.6	17.2	22.4
		Asia	206	24.8	21.3	28.9
	D-QIV-Y	Europe	197	11.7	10.1	13.5

				MGI		
					95% CI	
Strain	Group	Sub-group	N	Value	LL	UL
		Asia	35	11.9	8.0	17.5
A/Victoria/210/2009 (H3N2) (1/DIL)	D-QIV	US	323	8.3	7.3	9.4
		Europe	267	8.1	7.1	9.3
		Asia	200	7.0	6.0	8.3
	FLUARIX	US	328	6.4	5.6	7.2
		Europe	278	8.6	7.5	9.9
		Asia	212	7.0	6.0	8.2
	TIV-2	US	324	7.1	6.3	8.0
		Europe	270	8.6	7.5	9.8
		Asia	206	6.9	5.9	8.1
	D-QIV-Y	Europe	197	10.3	8.9	12.0
		Asia	35	10.7	7.2	15.8
B/Brisbane/60/2008 (Victoria) (1/DIL)	D-QIV	US	323	6.9	6.0	7.9
		Europe	267	8.4	7.2	9.7
		Asia	200	9.2	7.7	10.9
	FLUARIX	US	328	5.8	5.1	6.6
		Europe	278	10.2	8.8	11.8
		Asia	212	9.2	7.7	11.1
	TIV-2	US	324	2.4	2.1	2.7
		Europe	270	3.0	2.7	3.4
		Asia	206	2.6	2.3	3.0
	D-QIV-Y	Europe	197	9.7	8.3	11.2
		Asia	35	10.2	6.9	15.3
B/Brisbane/3/2007 (Yamagata) (1/DIL)	D-QIV	US	323	6.6	5.8	7.5
		Europe	267	7.3	6.3	8.5
		Asia	200	9.0	7.6	10.7
	FLUARIX	US	328	2.6	2.4	2.9
		Europe	278	3.3	2.9	3.7
		Asia	212	2.9	2.5	3.3
	TIV-2	US	324	5.9	5.2	6.8
		Europe	270	9.2	7.9	10.8
		Asia	206	8.7	7.4	10.3
	D-QIV-Y	Europe	197	12.9	10.9	15.3
		Asia	35	13.1	7.7	22.4

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received Fluarix
TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV
US=Subjects from the United States, Europe = Subjects from Germany, France and Czech Republic, Asia = Subjects from Philippines
N = Number of subjects with pre and post-vaccination results available
MGI= Mean Geometric increase in serum HI GMTs post-vaccination

Reviewer's comment:
The immunogenicity endpoints (SCR, SPR, GMT and MGI) have similar results for all regions for all four strains.

3.2.3.4 Immunogenicity Conclusion

The statistical analyses were performed on the ATP cohort for immunogenicity and on the TVC.

- The pre-specified immunological non-inferiority criteria for D-QIV versus TIV-1 (*Fluarix*) and TIV-2 in children 3 to 17 years old, at 28 days after last vaccination, was met for the three strains contained in each TIV formulation:

- in terms of GMT ratios, as the upper limit of the two sides 95% CI for the GMT ratio of TIV over D-QIV did not exceed 1.5, and,
- in terms of SCR differences, as the upper limit of the two sides 95% CI for the difference in SCR of TIV minus D-QIV did not exceed 10%.

- The pre-specified immunological superiority criteria for D-QIV versus TIV-1 (*Fluarix*) and TIV-2 in children 3 to 17 years old, at 28 days after last vaccination was met for the B strain not contained in each TIV formulation:
  - in terms of GMT ratios, as the lower limit of the two sides 95% CI for the GMT ratio of D-QIV over TIV was greater than 1, and,
  - in terms of SCR differences, as the lower limit of the two sides 95% CI for the difference in SCR of D-QIV over TIV was greater than 0%.

3.2.4 Safety Results

The analysis of safety was performed on the total vaccinated cohort (TVC), as defined in the protocol.

The number and percentage of subjects who received study vaccine doses is presented in table 102 below.

Table 102: Number and percentage of subjects who received study vaccine doses (TVC)

	D-QIV N = 915		FLUARIX N = 912		TIV-2 N = 911		D-QIV-Y N = 277		Total N = 3015	
Total number of doses received	n	%	n	%	n	%	n	%	n	%
1	418	45.7	411	45.1	409	44.9	15	5.4	1253	41.6
2	497	54.3	501	54.9	502	55.1	262	94.6	1762	58.4
Any	915	100	912	100	911	100	277	100	3015	100

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received TIV-1 (*Fluarix*)
TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV
N = number of subjects in each group or in total included in the considered cohort
n/% = number/percentage of subjects receiving the specified total number of doses
Any = number and percentage of subjects receiving at least one dose

The symptom sheets were returned for 98.8%, 98.5% and 99.8% of subjects in the D-QIV, Fluarix and TIV-2 groups, respectively, and for 99.8% in the D-QIV Young group.

3.2.4.1 Overall Incidence of Adverse Events, Solicited (local and general) and Unsolicited AEs

The overall incidence of solicited and unsolicited AEs during the 7-day post-vaccination period is presented in table 103 for any grade and table 104 for grade 3.

Table 103: Incidence and nature of symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (TVC).

	Any symptom	General symptoms	Local symptoms

					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	D-QIV	915	550	60.1	56.9	63.3	915	347	37.9	34.8	41.2	915	455	49.7	46.4	53.0
	FLUARIX	912	522	57.2	54.0	60.5	912	348	38.2	35.0	41.4	912	435	47.7	44.4	51.0
	TIV-2	911	531	58.3	55.0	61.5	911	324	35.6	32.5	38.8	911	432	47.4	44.1	50.7
	D-QIV-Y	277	187	67.5	61.6	73.0	277	139	50.2	44.1	56.2	277	129	46.6	40.6	52.6
Dose 2	D-QIV	497	238	47.9	43.4	52.4	497	144	29.0	25.0	33.2	497	189	38.0	33.7	42.5
	FLUARIX	501	225	44.9	40.5	49.4	501	125	25.0	21.2	29.0	501	177	35.3	31.1	39.7
	TIV-2	502	240	47.8	43.4	52.3	502	144	28.7	24.8	32.9	502	189	37.6	33.4	42.1
	D-QIV-Y	262	163	62.2	56.0	68.1	262	127	48.5	42.3	54.7	262	103	39.3	33.4	45.5
Overall/dose	D-QIV	1412	788	55.8	53.2	58.4	1412	491	34.8	32.3	37.3	1412	644	45.6	43.0	48.2
	FLUARIX	1413	747	52.9	50.2	55.5	1413	473	33.5	31.0	36.0	1413	612	43.3	40.7	45.9
	TIV-2	1413	771	54.6	51.9	57.2	1413	468	33.1	30.7	35.6	1413	621	43.9	41.3	46.6
	D-QIV-Y	539	350	64.9	60.7	69.0	539	266	49.4	45.1	53.7	539	232	43.0	38.8	47.3
Overall/subject	D-QIV	915	600	65.6	62.4	68.7	915	400	43.7	40.5	47.0	915	497	54.3	51.0	57.6
	FLUARIX	912	577	63.3	60.0	66.4	912	397	43.5	40.3	46.8	912	472	51.8	48.5	55.0
	TIV-2	911	582	63.9	60.7	67.0	911	391	42.9	39.7	46.2	911	475	52.1	48.8	55.4
	D-QIV-Y	277	216	78.0	72.6	82.7	277	178	64.3	58.3	69.9	277	150	54.2	48.1	60.1

For each dose and overall/subject:

- N= number of subjects with at least one administered dose
- n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

For overall/dose:

- N= number of administered doses
- n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered

For subjects 3 to 17 years old:

- Any solicited and unsolicited AEs were reported for 65.6%, 63.3% and 63.9% of subjects in the D-QIV, Fluarix and TIV-2 groups, respectively, with any grade 3 symptoms reported for 7.4%, 7.0% and 4.6%.
- Any general AEs were reported for 43.7%, 43.5% and 42.9% of subjects in the D-QIV, Fluarix and TIV-2 groups, respectively, with grade 3 general AEs reported for 4.2%, 4.3% and 2.9%.
- Any local AEs were reported for 54.3%, 51.8% and 52.1% of subjects in the D-QIV, Fluarix and TIV-2 groups, respectively, with grade 3 local AEs reported for 3.9%, 3.6% and 2.2% (table 104)

For subjects 6 to 35 months old receiving D-QIV (D-QIV Young group):

- Any solicited and unsolicited AEs were reported for 78.0% of subjects with grade 3 symptoms reported for 13.0%.
- Any general AEs were reported for 64.3% of subjects with grade 3 general AEs reported for 11.2%.
- Any local AEs were reported for 54.2% of subjects with grade 3 local AEs reported for 2.2%

Table 104: Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (TVC).

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	D-QIV	915	53	5.8	4.4	7.5	915	31	3.4	2.3	4.8	915	27	3.0	2.0	4.3

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
	FLUARIX	912	50	5.5	4.1	7.2	912	29	3.2	2.1	4.5	912	27	3.0	2.0	4.3
	TIV-2	911	29	3.2	2.1	4.5	911	19	2.1	1.3	3.2	911	13	1.4	0.8	2.4
	D-QIV-Y	277	22	7.9	5.0	11.8	277	18	6.5	3.9	10.1	277	5	1.8	0.6	4.2
Dose 2	D-QIV	497	17	3.4	2.0	5.4	497	7	1.4	0.6	2.9	497	11	2.2	1.1	3.9
	FLUARIX	501	17	3.4	2.0	5.4	501	11	2.2	1.1	3.9	501	8	1.6	0.7	3.1
	TIV-2	502	13	2.6	1.4	4.4	502	7	1.4	0.6	2.9	502	7	1.4	0.6	2.9
	D-QIV-Y	262	20	7.6	4.7	11.5	262	19	7.3	4.4	11.1	262	1	0.4	0.0	2.1
Overall/dose	D-QIV	1412	70	5.0	3.9	6.2	1412	38	2.7	1.9	3.7	1412	38	2.7	1.9	3.7
	FLUARIX	1413	67	4.7	3.7	6.0	1413	40	2.8	2.0	3.8	1413	35	2.5	1.7	3.4
	TIV-2	1413	42	3.0	2.2	4.0	1413	26	1.8	1.2	2.7	1413	20	1.4	0.9	2.2
	D-QIV-Y	539	42	7.8	5.7	10.4	539	37	6.9	4.9	9.3	539	6	1.1	0.4	2.4
Overall/subject	D-QIV	915	68	7.4	5.8	9.3	915	38	4.2	3.0	5.7	915	36	3.9	2.8	5.4
	FLUARIX	912	64	7.0	5.4	8.9	912	39	4.3	3.1	5.8	912	33	3.6	2.5	5.0
	TIV-2	911	42	4.6	3.3	6.2	911	26	2.9	1.9	4.2	911	20	2.2	1.3	3.4
	D-QIV-Y	277	36	13.0	9.3	17.5	277	31	11.2	7.7	15.5	277	6	2.2	0.8	4.7

For each dose and overall/subject:

- N= number of subjects with at least one administered dose
- n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

For overall/dose:

- N= number of administered doses
- n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered

3.2.4.1.1 Solicited Local Adverse Events

For subjects 3 to 17 years old:

- Injection site pain was the most frequently reported local AE across the three treatment groups (reported for 49.2%, 47.1% and 45.9% of subjects in the D-QIV, Fluarix and TIV-2 groups, respectively). Redness was reported for 22.7% to 24.9% of subjects and swelling for 17.7% to 21.7%. Grade 3 local pain was reported for 2.2%, 2.3% and 1.4% of subjects in the D-QIV, Fluarix and TIV-2 groups, respectively, grade 3 redness for 1.3%, 0.3% and 0.7% of subjects and grade 3 swelling for 1.2%, 1.1% and 0.3% of subjects.
- The median duration of solicited local AEs ranged between 1.0 and 2.0 days for all groups.

For subjects 6 to 35 months old receiving D-QIV (D-QIV Young group):

- Injection site pain and redness were the most frequently reported local AEs (reported for 41.9% and 36.1% of subjects, respectively). Grade 3 local pain and grade 3 redness were reported for 1.8% and 0.4% of subjects. No grade 3 swelling was reported.
- The median duration of solicited local AEs ranged between 1.0 and 2.0 days for all groups.

3.2.4.1.2 Solicited General Adverse Events

For subjects 3 to 5 years old:

- Drowsiness (23.0%, 17.5% and 21.1% of subjects in the D-QIV, Fluarix and TIV-2 groups) and irritability (22.3%, 17.8% and 18.9%) were the most frequently reported general AEs across the three treatment groups followed by loss of appetite (20.3%,12.7% and 16.8%) and temperature ≥37.5°C (17.2%, 16.2% and 14.6%).
- Grade 3 solicited general AEs, including fever > 39.0°C, were reported for less than 1.7% of subjects.
- The median duration of solicited general AEs ranged between 1.0 and 3.0 days for the D-QIV group and between 1.0 and 2.0 days for the Fluarix and TIV-2 groups.

For subjects 6 to 17 years old:

- Fatigue (21.0%, 20.0% and 18.2% of subjects in the D-QIV, Fluarix and TIV-2 groups), headache (17.9%, 21.2% and 18.2%) and muscle aches (18.9%, 18.0% and 16.9%) were the most frequently reported general AEs across the three groups.
- Grade 3 solicited general AEs, including fever > 39.0°C, were reported for less than 1.5% of subjects.
- The median duration of solicited general AEs ranged between 1.0 and 2.0 days for the three groups.

For subjects 6 to 35 months old receiving D-QIV (D-QIV Young group):

- Irritability (43.0%) was the most frequently reported general AE followed by drowsiness (30.3%), loss of appetite (30.0%) and temperature ≥37.5°C (29.2%) of subjects.
- The most frequently reported grade 3 general AE were fever > 39.0°C (6.5% of subjects), loss of appetite (4.3%), irritability (4.0%) and drowsiness (2.5%).
- The median duration of solicited general AEs ranged between 1.0 and 3.0 days.

3.2.4.1.3 Unsolicited Adverse Events

For subjects 3 to 17 years old:

- 284 subjects (31.0%) from the D-QIV group, 305 (33.4%) from the Fluarix group and 308 (33.8%) from the TIV-2 group experienced at least one unsolicited AE during the 28-day post-vaccination period. Nasopharyngitis was the most frequently reported unsolicited AE (5.4%, 6.6% and 7.0%). Grade 3 unsolicited AE were reported as follows: 29 events reported for 20 subjects (2.2%) from the D-QIV group, 51 events for 37 (4.1%) from the Fluarix group and 35 events for 26 (2.9%) from the TIV-2 group.
- 18 subjects (2.0%) from the D-QIV group, 19 (2.1%) from the Fluarix group and 23 (2.5%) from the TIV-2 group experienced 28, 35 and 28 unsolicited AEs considered as related to vaccination during the 28-day post-vaccination period.
- During the entire study period, 271 subjects (29.6%) from the D-QIV group, 278 (30.5%) from the Fluarix group and 303 (33.3%) from the TIV-2 group experienced 507, 474 and 547 unsolicited AEs with medically attended visit (MAV). Nasopharyngitis was the most frequently reported unsolicited AE with MAV (4.3%, 4.7% and 6.1%).
- Two subjects (0.2%) from the D-QIV group, 4 (0.4%) from the Fluarix group and 4 (0.4%) from the TIV-2 group experienced 2, 5 and 4 unsolicited AEs considered as related to vaccination with MAV during the entire study period.

For subjects 6 to 35 months old receiving D-QIV (D-QIV Young group):

- 167 subjects (60.3%) experienced at least one unsolicited AE during the 28-day post-vaccination period. Nasopharyngitis was the most frequently reported unsolicited AE (13.4%). 22 grade 3 unsolicited AEs were reported for 20 subjects (7.2%).
- Five subjects (1.8%) experienced 5 unsolicited AEs considered as related to vaccination during the 28-day post-vaccination period.
- 171 subjects (61.7%) experienced 447 unsolicited AEs with MAV during the entire study period. Nasopharyngitis was the most frequently reported unsolicited AE with MAV (9.0%).
- Two subjects (0.7%) experienced 2 unsolicited AEs considered as related to vaccination with MAV during the entire study period (rhinotracheitis and febrile infection)

3.2.4.2 Series Adverse Events

The global summaries of SAE reported within the 28-day post-vaccination period and during the entire study period, are presented in table 105 and table 106

Table 105: Global Summary of serious adverse event reported within the 28-day (Days 0-27) (Days 0-27 for all subjects and Days 28-55 for unprimed subjects) post-vaccination period (TVC)

	Group				
	D-QIV	FLUARIX	TIV-2	D-QIV-Y	Total
Number of subjects with at least one unsolicited symptom reported	1	1	1	7	10
Number of doses followed by at least unsolicited symptom SAE	1	1	1	7	10
Number of unsolicited symptoms classified by MedDRA Preferred Term*	1	2	1	10	14
Number of unsolicited symptoms reported	1	2	1	10	14

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received TIV-1 (*Fluarix*)
TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV
* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once

Table 106: Global Summary of serious adverse event reported during the entire study period (TVC)

	Group				
	D-QIV	FLUARIX	TIV-2	D-QIV-Y	Total
Number of subjects with at least one unsolicited symptom reported	8	6	7	9	30
Number of doses followed by at least one unsolicited symptom	8	6	7	9	30
Number of unsolicited symptoms classified by MedDRA Preferred Term*	12	7	8	16	43
Number of unsolicited symptoms reported	12	7	8	18	45

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received TIV-1 (*Fluarix*)
TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV
* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once

For subjects 3 to 17 years old:

- Eight (0.9%) subjects from the D-QIV group, 6 (0.7%) from the Fluarix group and 7 (0.8%) from the TIV-2 group reported 12, 7 and 8 SAEs, respectively, during the entire study period.
- None of these SAEs were considered as related to vaccination.

For subjects 6 to 35 months old receiving D-QIV (D-QIV Young group):

- Nine (1.5%) subjects reported 18 SAEs during the entire study period.
- None of these SAEs were considered as related to vaccination.

3.2.4.3 Adverse Events leading to premature discontinuation of study vaccine and/or study

Overall, three subjects discontinued the study due to AE/SAE.

- Two subjects (one from the D-QIV and one from the Fluarix group) discontinued the study due to a SAE:
  - A 5-year old subject experienced bacterial enteritis 14 days after having received the first dose of D-QIV vaccine.
  - A 3-year old subject died due to a road traffic accident 4 months after having received the second dose of Fluarix.

None of those were considered as related to vaccination.

- One subject from the Fluarix group discontinued the study due to a non-serious AE (viral pneumonia).

3.2.4.4 Other Significant Adverse Events

3.2.4.4.1 Potential Immune-Mediated Diseases (pIMD)

The global summary of potential Immune-Mediated Disease (pIMD) reported during the entire study period is presented in table 107

Table 107: Global Summary of potential Immune-Mediated Disease (pIMD) reported during the entire study period (TVC)

	Group				
	D-QIV	FLUARIX	TIV-2	D-QIV-Y	Total
Number of subjects with at least one pIMD reported	0	0	2	0	2
Number of doses followed by at least one pIMD	0	0	2	0	2
Number of pIMDs classified by MedDRA Preferred Term*	0	0	2	0	2
Number of pIMDs reported	0	0	2	0	2

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received TIV-1 (*Fluarix*)
TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV
* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once

Two pIMDs were reported for two subjects from the TIV-2 group.

- A 14-year old female subject with a history of headache and upper respiratory symptoms 1 week prior to event onset developed non-serious Bell's palsy 91 days post-vaccination. The event resolved spontaneously approximately 3 weeks after onset.
- An 11-year-old female subject with a family history of diabetes (unspecified type), developed type 1 diabetes mellitus 42 days post vaccination. Following treatment, the event "resolved with sequelae" approximately 3 weeks after onset.

None of these pIMDs were considered with causal relationship to vaccination.

3.2.4.4.2 Febrile Convulsion Cases

Two cases of febrile convulsion were reported for two subjects from the D-QIV Young group. Both cases occurred after the 2-day enhanced surveillance period and were considered serious and unrelated to vaccination by the investigator.

- A 35-month-old male subject experienced a febrile convulsion during a viral infection 16 days after the first dose of vaccine and recovered the same day after treatment. Subsequent study vaccine administration was discontinued.
- A 14-month-old male subject experienced a febrile convulsion along with mild symptoms of a febrile viral otitis media 98 days after the second dose of vaccine and recovered the same day after treatment.

3.2.4.5 Concomitant Medication

For subjects 3 to 17 years old:

- During the 28-day post-vaccination period, concomitant medication was taken by 32.3% of subjects in the D-QIV group, 30.4% in the Fluarix group and 33.8% of subjects in the TIV-2 group. Overall, 14.5% of subjects in the D-QIV group, 16.1% in the Fluarix group and 16.4% in the TIV-2 group took antipyretic medication.
- Two subjects from the D-QIV group, 3 subjects from the Fluarix group and 3 subjects from the TIV-2 group took prophylactic antipyretic medication after Dose 1. One subject from the Fluarix group and one subject from the TIV-2 group took prophylactic antipyretic medication after Dose 2.

For subjects 6 to 35 months old receiving D-QIV (D-QIV Young group):

- During the 28-day post-vaccination period, concomitant medication was taken by 65.7% of subjects. Overall, 30.3% of subjects took antipyretic medication.
- No subject took prophylactic antipyretic medication after Dose 1 and one subject took such medication after Dose 2.

3.2.4.6 Subgroup Analysis of Safety

Analysis by Age

Overall incidence and nature of solicited and unsolicited AEs (any grade and grade 3) during the 7-Day post-vaccination period analyzed by age strata are presented in table 108 (any grade) and table 109 (grade 3).

Table 108: Incidence and nature of symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall by age (TVC)

			Any symptom					General symptoms					Local symptoms				
						95% CI					95% CI					95% CI	
	Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	D-QIV	3 - 8 years	598	339	56.7	52.6	60.7	598	213	35.6	31.8	39.6	598	276	46.2	42.1	50.2
		9 - 17 years	317	211	66.6	61.1	71.7	317	134	42.3	36.8	47.9	317	179	56.5	50.8	62.0
	FLUARIX	3 - 8 years	596	325	54.5	50.4	58.6	596	204	34.2	30.4	38.2	596	262	44.0	39.9	48.1

			Any symptom					General symptoms					Local symptoms				
						95% CI					95% CI					95% CI	
	Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
		9 - 17 years	316	197	62.3	56.7	67.7	316	144	45.6	40.0	51.2	316	173	54.7	49.1	60.3
	TIV-2	18 - 35 months	1	1	100	2.5	100	1	1	100	2.5	100	1	1	100	2.5	100
		3 - 8 years	597	342	57.3	53.2	61.3	597	202	33.8	30.0	37.8	597	273	45.7	41.7	49.8
		9 - 17 years	313	188	60.1	54.4	65.5	313	121	38.7	33.2	44.3	313	158	50.5	44.8	56.2
	D-QIV-Y	6 - 17 months	86	59	68.6	57.7	78.2	86	46	53.5	42.4	64.3	86	31	36.0	26.0	47.1
		18 - 35 months	191	128	67.0	59.9	73.6	191	93	48.7	41.4	56.0	191	98	51.3	44.0	58.6
Dose 2	D-QIV	3 - 8 years	497	238	47.9	43.4	52.4	497	144	29.0	25.0	33.2	497	189	38.0	33.7	42.5
	FLUARIX	3 - 8 years	501	225	44.9	40.5	49.4	501	125	25.0	21.2	29.0	501	177	35.3	31.1	39.7
	TIV-2	18 - 35 months	1	1	100	2.5	100	1	1	100	2.5	100	1	1	100	2.5	100
		3 - 8 years	501	239	47.7	43.3	52.2	501	143	28.5	24.6	32.7	501	188	37.5	33.3	41.9
	D-QIV-Y	6 - 17 months	85	58	68.2	57.2	77.9	85	48	56.5	45.3	67.2	85	27	31.8	22.1	42.8
		18 - 35 months	177	105	59.3	51.7	66.6	177	79	44.6	37.2	52.3	177	76	42.9	35.5	50.6
Overall/dose	D-QIV	3 - 8 years	1095	577	52.7	49.7	55.7	1095	357	32.6	29.8	35.5	1095	465	42.5	39.5	45.5
		9 - 17 years	317	211	66.6	61.1	71.7	317	134	42.3	36.8	47.9	317	179	56.5	50.8	62.0
	FLUARIX	3 - 8 years	1097	550	50.1	47.1	53.1	1097	329	30.0	27.3	32.8	1097	439	40.0	37.1	43.0
		9 - 17 years	316	197	62.3	56.7	67.7	316	144	45.6	40.0	51.2	316	173	54.7	49.1	60.3
	TIV-2	18 - 35 months	2	2	100	15.8	100	2	2	100	15.8	100	2	2	100	15.8	100
		3 - 8 years	1098	581	52.9	49.9	55.9	1098	345	31.4	28.7	34.3	1098	461	42.0	39.0	45.0
		9 - 17 years	313	188	60.1	54.4	65.5	313	121	38.7	33.2	44.3	313	158	50.5	44.8	56.2
	D-QIV-Y	6 - 17 months	171	117	68.4	60.9	75.3	171	94	55.0	47.2	62.6	171	58	33.9	26.9	41.5
		18 - 35 months	368	233	63.3	58.2	68.3	368	172	46.7	41.5	52.0	368	174	47.3	42.1	52.5
Overall/subject	D-QIV	3 - 8 years	598	389	65.1	61.1	68.9	598	266	44.5	40.5	48.6	598	318	53.2	49.1	57.2
		9 - 17 years	317	211	66.6	61.1	71.7	317	134	42.3	36.8	47.9	317	179	56.5	50.8	62.0
	FLUARIX	3 - 8 years	596	380	63.8	59.8	67.6	596	253	42.4	38.4	46.5	596	299	50.2	46.1	54.3
		9 - 17 years	316	197	62.3	56.7	67.7	316	144	45.6	40.0	51.2	316	173	54.7	49.1	60.3
	TIV-2	18 - 35 months	1	1	100	2.5	100	1	1	100	2.5	100	1	1	100	2.5	100
		3 - 8 years	597	393	65.8	61.9	69.6	597	269	45.1	41.0	49.1	597	316	52.9	48.8	57.0
		9 - 17 years	313	188	60.1	54.4	65.5	313	121	38.7	33.2	44.3	313	158	50.5	44.8	56.2
	D-QIV-Y	6 - 17 months	86	70	81.4	71.6	89.0	86	61	70.9	60.1	80.2	86	38	44.2	33.5	55.3
		18 - 35 months	191	146	76.4	69.8	82.3	191	117	61.3	54.0	68.2	191	112	58.6	51.3	65.7

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received TIV-1 (*Fluarix*)

TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV

For each dose and overall/subject:

- N= number of subjects with at least one administered dose
- n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

Similar results were observed for both age strata for subjects 3 to 17 years old. For example any solicited and unsolicited AEs were reported for 65.1%, 63.8% and 65.8% of subjects in the D-QIV, Fluarix and TIV-2 groups, respectively for the sub group 3-8 years old compared to 66.6%, 62.3%, 60.1% for the 9-17 years old sub group.

For subjects 6 to 35 months old receiving D-QIV (D-QIV Young group) a relatively higher differences were observed in the two sub groups (6-17 months old and 18-35 months) (81.4 % versus 76.4% for any symptom, 70.9% versus 61.3% for general symptoms and 44.2% versus 58.6% for local symptoms)

Table 109: Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period following each

dose and overall by age (TVC)

			Any symptom					General symptoms					Local symptoms				
						95% CI					95% CI					95% CI	
	Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	D-QIV	3 - 8 years	598	34	5.7	4.0	7.9	598	19	3.2	1.9	4.9	598	19	3.2	1.9	4.9
		9 - 17 years	317	19	6.0	3.6	9.2	317	12	3.8	2.0	6.5	317	8	2.5	1.1	4.9
	FLUARIX	3 - 8 years	596	27	4.5	3.0	6.5	596	16	2.7	1.5	4.3	596	13	2.2	1.2	3.7
		9 - 17 years	316	23	7.3	4.7	10.7	316	13	4.1	2.2	6.9	316	14	4.4	2.4	7.3
	TIV-2	18 - 35 months	1	0	0.0	0.0	97.5	1	0	0.0	0.0	97.5	1	0	0.0	0.0	97.5
		3 - 8 years	597	13	2.2	1.2	3.7	597	9	1.5	0.7	2.8	597	4	0.7	0.2	1.7
		9 - 17 years	313	16	5.1	2.9	8.2	313	10	3.2	1.5	5.8	313	9	2.9	1.3	5.4
	D-QIV-Y	6 - 17 months	86	8	9.3	4.1	17.5	86	7	8.1	3.3	16.1	86	1	1.2	0.0	6.3
		18 - 35 months	191	14	7.3	4.1	12.0	191	11	5.8	2.9	10.1	191	4	2.1	0.6	5.3
Dose 2	D-QIV	3 - 8 years	497	17	3.4	2.0	5.4	497	7	1.4	0.6	2.9	497	11	2.2	1.1	3.9
	FLUARIX	3 - 8 years	501	17	3.4	2.0	5.4	501	11	2.2	1.1	3.9	501	8	1.6	0.7	3.1
	TIV-2	18 - 35 months	1	0	0.0	0.0	97.5	1	0	0.0	0.0	97.5	1	0	0.0	0.0	97.5
		3 - 8 years	501	13	2.6	1.4	4.4	501	7	1.4	0.6	2.9	501	7	1.4	0.6	2.9
	D-QIV-Y	6 - 17 months	85	9	10.6	5.0	19.2	85	9	10.6	5.0	19.2	85	0	0.0	0.0	4.2
		18 - 35 months	177	11	6.2	3.1	10.8	177	10	5.6	2.7	10.1	177	1	0.6	0.0	3.1
Overall/dose	D-QIV	3 - 8 years	1095	51	4.7	3.5	6.1	1095	26	2.4	1.6	3.5	1095	30	2.7	1.9	3.9
		9 - 17 years	317	19	6.0	3.6	9.2	317	12	3.8	2.0	6.5	317	8	2.5	1.1	4.9
	FLUARIX	3 - 8 years	1097	44	4.0	2.9	5.3	1097	27	2.5	1.6	3.6	1097	21	1.9	1.2	2.9
		9 - 17 years	316	23	7.3	4.7	10.7	316	13	4.1	2.2	6.9	316	14	4.4	2.4	7.3
	TIV-2	18 - 35 months	2	0	0.0	0.0	84.2	2	0	0.0	0.0	84.2	2	0	0.0	0.0	84.2
		3 - 8 years	1098	26	2.4	1.6	3.5	1098	16	1.5	0.8	2.4	1098	11	1.0	0.5	1.8
		9 - 17 years	313	16	5.1	2.9	8.2	313	10	3.2	1.5	5.8	313	9	2.9	1.3	5.4
	D-QIV-Y	6 - 17 months	171	17	9.9	5.9	15.4	171	16	9.4	5.4	14.7	171	1	0.6	0.0	3.2
		18 - 35 months	368	25	6.8	4.4	9.9	368	21	5.7	3.6	8.6	368	5	1.4	0.4	3.1
Overall/subject	D-QIV	3 - 8 years	598	49	8.2	6.1	10.7	598	26	4.3	2.9	6.3	598	28	4.7	3.1	6.7
		9 - 17 years	317	19	6.0	3.6	9.2	317	12	3.8	2.0	6.5	317	8	2.5	1.1	4.9
	FLUARIX	3 - 8 years	596	41	6.9	5.0	9.2	596	26	4.4	2.9	6.3	596	19	3.2	1.9	4.9
		9 - 17 years	316	23	7.3	4.7	10.7	316	13	4.1	2.2	6.9	316	14	4.4	2.4	7.3
	TIV-2	18 - 35 months	1	0	0.0	0.0	97.5	1	0	0.0	0.0	97.5	1	0	0.0	0.0	97.5
		3 - 8 years	597	26	4.4	2.9	6.3	597	16	2.7	1.5	4.3	597	11	1.8	0.9	3.3
		9 - 17 years	313	16	5.1	2.9	8.2	313	10	3.2	1.5	5.8	313	9	2.9	1.3	5.4
	D-QIV-Y	6 - 17 months	86	14	16.3	9.2	25.8	86	13	15.1	8.3	24.5	86	1	1.2	0.0	6.3
		18 - 35 months	191	22	11.5	7.4	16.9	191	18	9.4	5.7	14.5	191	5	2.6	0.9	6.0

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received TIV-1 (*Fluarix*)

TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV

For each dose and overall/subject:

- N= number of subjects with at least one administered dose
- n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

For overall/dose:

- N= number of administered doses
- n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered

Analysis by Gender

Overall incidence and nature of solicited and unsolicited AEs (any grade and grade 3) during the 7-Day post-vaccination period analyzed by gender are presented in table 110 (any grade) and table 111 (grade 3).

Table 110: Incidence and nature of symptoms (solicited and unsolicited) reported during

the 7-day (Days 0-6) post-vaccination period following each dose and overall by gender (TVC)

			Any symptom					General symptoms					Local symptoms				
						95% CI					95% CI					95% CI	
	Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	D-QIV	Male	472	277	58.7	54.1	63.2	472	173	36.7	32.3	41.2	472	230	48.7	44.1	53.3
		Female	443	273	61.6	56.9	66.2	443	174	39.3	34.7	44.0	443	225	50.8	46.0	55.5
	FLUARIX	Male	473	266	56.2	51.6	60.8	473	175	37.0	32.6	41.5	473	217	45.9	41.3	50.5
		Female	439	256	58.3	53.5	63.0	439	173	39.4	34.8	44.2	439	218	49.7	44.9	54.4
	TIV-2	Male	471	279	59.2	54.6	63.7	471	171	36.3	32.0	40.8	471	219	46.5	41.9	51.1
		Female	440	252	57.3	52.5	61.9	440	153	34.8	30.3	39.4	440	213	48.4	43.7	53.2
	D-QIV-Y	Male	159	109	68.6	60.7	75.7	159	84	52.8	44.8	60.8	159	78	49.1	41.1	57.1
		Female	118	78	66.1	56.8	74.6	118	55	46.6	37.4	56.0	118	51	43.2	34.1	52.7
Dose 2	D-QIV	Male	252	113	44.8	38.6	51.2	252	69	27.4	22.0	33.3	252	92	36.5	30.6	42.8
		Female	245	125	51.0	44.6	57.4	245	75	30.6	24.9	36.8	245	97	39.6	33.4	46.0
	FLUARIX	Male	268	110	41.0	35.1	47.2	268	60	22.4	17.5	27.9	268	87	32.5	26.9	38.4
		Female	233	115	49.4	42.8	56.0	233	65	27.9	22.2	34.1	233	90	38.6	32.3	45.2
	TIV-2	Male	260	127	48.8	42.6	55.1	260	74	28.5	23.1	34.4	260	98	37.7	31.8	43.9
		Female	242	113	46.7	40.3	53.2	242	70	28.9	23.3	35.1	242	91	37.6	31.5	44.0
	D-QIV-Y	Male	150	91	60.7	52.4	68.5	150	73	48.7	40.4	57.0	150	53	35.3	27.7	43.5
		Female	112	72	64.3	54.7	73.1	112	54	48.2	38.7	57.9	112	50	44.6	35.2	54.3
Overall/dose	D-QIV	Male	724	390	53.9	50.2	57.5	724	242	33.4	30.0	37.0	724	322	44.5	40.8	48.2
		Female	688	398	57.8	54.1	61.6	688	249	36.2	32.6	39.9	688	322	46.8	43.0	50.6
	FLUARIX	Male	741	376	50.7	47.1	54.4	741	235	31.7	28.4	35.2	741	304	41.0	37.5	44.7
		Female	672	371	55.2	51.4	59.0	672	238	35.4	31.8	39.2	672	308	45.8	42.0	49.7
	TIV-2	Male	731	406	55.5	51.9	59.2	731	245	33.5	30.1	37.1	731	317	43.4	39.7	47.0
		Female	682	365	53.5	49.7	57.3	682	223	32.7	29.2	36.4	682	304	44.6	40.8	48.4
	D-QIV-Y	Male	309	200	64.7	59.1	70.1	309	157	50.8	45.1	56.5	309	131	42.4	36.8	48.1
		Female	230	150	65.2	58.7	71.4	230	109	47.4	40.8	54.1	230	101	43.9	37.4	50.6
Overall/subject	D-QIV	Male	472	300	63.6	59.0	67.9	472	199	42.2	37.7	46.8	472	249	52.8	48.1	57.3
		Female	443	300	67.7	63.1	72.1	443	201	45.4	40.7	50.1	443	248	56.0	51.2	60.7
	FLUARIX	Male	473	291	61.5	57.0	65.9	473	198	41.9	37.4	46.5	473	235	49.7	45.1	54.3
		Female	439	286	65.1	60.5	69.6	439	199	45.3	40.6	50.1	439	237	54.0	49.2	58.7
	TIV-2	Male	471	298	63.3	58.7	67.6	471	197	41.8	37.3	46.4	471	238	50.5	45.9	55.1
		Female	440	284	64.5	59.9	69.0	440	194	44.1	39.4	48.9	440	237	53.9	49.1	58.6
	D-QIV-Y	Male	159	126	79.2	72.1	85.3	159	105	66.0	58.1	73.4	159	87	54.7	46.6	62.6
		Female	118	90	76.3	67.6	83.6	118	73	61.9	52.5	70.6	118	63	53.4	44.0	62.6

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received TIV-1 (*Fluarix*)

TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV

For each dose and overall/subject:

- N= number of subjects with at least one administered dose
- n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

For overall/dose:

- N= number of administered doses
- n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered

Table 111: Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall by gender (TVC).

			Any symptom					General symptoms					Local symptoms				
						95% CI					95% CI					95% CI	
	Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL

			Any symptom					General symptoms					Local symptoms				
						95% CI					95% CI					95% CI	
	Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	D-QIV	Male	472	32	6.8	4.7	9.4	472	18	3.8	2.3	6.0	472	16	3.4	1.9	5.4
		Female	443	21	4.7	3.0	7.2	443	13	2.9	1.6	5.0	443	11	2.5	1.2	4.4
	FLUARIX	Male	473	23	4.9	3.1	7.2	473	14	3.0	1.6	4.9	473	13	2.7	1.5	4.7
		Female	439	27	6.2	4.1	8.8	439	15	3.4	1.9	5.6	439	14	3.2	1.8	5.3
	TIV-2	Male	471	15	3.2	1.8	5.2	471	10	2.1	1.0	3.9	471	6	1.3	0.5	2.8
		Female	440	14	3.2	1.8	5.3	440	9	2.0	0.9	3.8	440	7	1.6	0.6	3.3
	D-QIV-Y	Male	159	14	8.8	4.9	14.3	159	12	7.5	4.0	12.8	159	3	1.9	0.4	5.4
		Female	118	8	6.8	3.0	12.9	118	6	5.1	1.9	10.7	118	2	1.7	0.2	6.0
Dose 2	D-QIV	Male	252	7	2.8	1.1	5.6	252	2	0.8	0.1	2.8	252	5	2.0	0.6	4.6
		Female	245	10	4.1	2.0	7.4	245	5	2.0	0.7	4.7	245	6	2.4	0.9	5.3
	FLUARIX	Male	268	11	4.1	2.1	7.2	268	9	3.4	1.5	6.3	268	4	1.5	0.4	3.8
		Female	233	6	2.6	1.0	5.5	233	2	0.9	0.1	3.1	233	4	1.7	0.5	4.3
	TIV-2	Male	260	7	2.7	1.1	5.5	260	5	1.9	0.6	4.4	260	3	1.2	0.2	3.3
		Female	242	6	2.5	0.9	5.3	242	2	0.8	0.1	3.0	242	4	1.7	0.5	4.2
	D-QIV-Y	Male	150	13	8.7	4.7	14.4	150	12	8.0	4.2	13.6	150	1	0.7	0.0	3.7
		Female	112	7	6.3	2.5	12.5	112	7	6.3	2.5	12.5	112	0	0.0	0.0	3.2
Overall/dose	D-QIV	Male	724	39	5.4	3.9	7.3	724	20	2.8	1.7	4.2	724	21	2.9	1.8	4.4
		Female	688	31	4.5	3.1	6.3	688	18	2.6	1.6	4.1	688	17	2.5	1.4	3.9
	FLUARIX	Male	741	34	4.6	3.2	6.4	741	23	3.1	2.0	4.6	741	17	2.3	1.3	3.6
		Female	672	33	4.9	3.4	6.8	672	17	2.5	1.5	4.0	672	18	2.7	1.6	4.2
	TIV-2	Male	731	22	3.0	1.9	4.5	731	15	2.1	1.2	3.4	731	9	1.2	0.6	2.3
		Female	682	20	2.9	1.8	4.5	682	11	1.6	0.8	2.9	682	11	1.6	0.8	2.9
	D-QIV-Y	Male	309	27	8.7	5.8	12.5	309	24	7.8	5.0	11.3	309	4	1.3	0.4	3.3
		Female	230	15	6.5	3.7	10.5	230	13	5.7	3.0	9.5	230	2	0.9	0.1	3.1
Overall/subject	D-QIV	Male	472	39	8.3	5.9	11.1	472	20	4.2	2.6	6.5	472	21	4.4	2.8	6.7
		Female	443	29	6.5	4.4	9.3	443	18	4.1	2.4	6.3	443	15	3.4	1.9	5.5
	FLUARIX	Male	473	34	7.2	5.0	9.9	473	23	4.9	3.1	7.2	473	17	3.6	2.1	5.7
		Female	439	30	6.8	4.7	9.6	439	16	3.6	2.1	5.9	439	16	3.6	2.1	5.9
	TIV-2	Male	471	22	4.7	3.0	7.0	471	15	3.2	1.8	5.2	471	9	1.9	0.9	3.6
		Female	440	20	4.5	2.8	6.9	440	11	2.5	1.3	4.4	440	11	2.5	1.3	4.4
	D-QIV-Y	Male	159	23	14.5	9.4	20.9	159	20	12.6	7.9	18.8	159	4	2.5	0.7	6.3
		Female	118	13	11.0	6.0	18.1	118	11	9.3	4.7	16.1	118	2	1.7	0.2	6.0

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received TIV-1 (*Fluarix*)

TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV

For each dose and overall/subject:

- N= number of subjects with at least one administered dose
- n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

For overall/dose:

- N= number of administered doses
- n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered

The percentage of subjects reporting solicited and unsolicited AEs were similar for both males and females in the D-QIV, Fluarix and TIV-2 for any grade (table 110) and grade 3(table 111)

Analysis by Race

The number and percentage of subjects who received the study vaccine dose by race is presented in table 112.

Table 112: Number and percentage of subjects who received the study vaccine dose by race (TVC)

	D-QIV				FLUARIX				TIV-2				D-QIV-Y				Total			
	W/C N = 493		NW/C N=422		W/C N = 478		NW/C N = 434		W/C N = 486		NW/C N = 425		W/C N = 193		NW/C N = 84		W/C N = 1650		NW/C N = 1365	
Total number of doses received	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
1	256	51.9	162	38.4	242	50.6	169	38.9	250	51.4	159	37.4	12	6.2	3	3.6	760	46.1	493	36.1
2	237	48.1	260	61.6	236	49.4	265	61.1	236	48.6	266	62.6	181	93.8	81	96.4	890	53.9	872	63.9
Any	493	100	422	100	478	100	434	100	486	100	425	100	193	100	84	100	1650	100	1365	100

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received Fluarix,
TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV
W/C = White/Caucasian subjects, NW/C = Non-White/Caucasian subjects
N = number of subjects in each group or in total included in the considered cohort
n/% = number/percentage of subjects receiving the specified total number of doses
Any = number and percentage of subjects receiving at least one dose

Overall incidence and nature of solicited and unsolicited AEs (any grade and grade 3) during the 7-Day post-vaccination period analyzed by race (White/Caucasian versus Non-White/Caucasian) are presented in table 113 (any grade) and table 114 (grade 3).

Relatively higher percentage of subjects in the White/Caucasian sub group report incidence of solicited and unsolicited AEs compared to Non-White/Caucasian sub-group for D-QIV, Fluarix and TIV-2 groups:

D-QIV group:

- Any grade: 76.5% versus 52.8% for any symptom, 51.3% versus 34.8% general symptom, 67.3% versus 39.1% (table 113)
- Grade 3: 11.4% versus 2.8% for any symptom, 6.1% versus 1.9% general symptom, 6.1% versus 1.4% (table 114)

Fluarix:

- Any grade: 77% versus 48.2% for any symptom, 53.6% % versus 32.5% general symptom, 68.2% versus 33.6% (table 113)
- Grade 3: 7.3% versus 2.3% for any symptom, 6.1% versus 2.3% general symptom, 5.0% versus 2.1% (table 114)

TIV-2:

- Any grade: 78.8% versus 46.8% for any symptom, 53.7% % versus 30.6% general symptom, 66.3% versus 36% (table 113)
- Grade 3: 4.5% versus 1.1% for any symptom, 3.9% versus 1.6% general symptom, 3.1% versus 1.2% (table 114)

Table 113: Incidence and nature of symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period following each dose and

overall by race (TVC)

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received Fluarix

			Any symptom					General symptoms					Local symptoms				
						95% CI					95% CI					95% CI	
	Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	D-QIV	W/C	493	360	73	68.9	76.9	493	228	46.2	41.8	50.8	493	315	63.9	59.5	68.1
		Non- W/C	422	190	45	40.2	49.9	422	119	28.2	24	32.8	422	140	33.2	28.7	37.9
	FLUARIX	W/C	478	342	71.5	67.3	75.6	478	230	48.1	43.6	52.7	478	306	64	59.5	68.3
		Non- W/C	434	180	41.5	36.8	46.3	434	118	27.2	23.1	31.6	434	129	29.7	25.5	34.3
	TIV-2	W/C	486	364	74.9	70.8	78.7	486	230	47.3	42.8	51.9	486	303	62.3	57.9	66.7
		Non- W/C	425	167	39.3	34.6	44.1	425	94	22.1	18.3	26.4	425	129	30.4	26	35
	D-QIV-Y	W/C	193	146	75.6	69	81.5	193	110	57	49.7	64.1	193	104	53.9	46.6	61.1
		Non- W/C	84	41	48.8	37.7	60	84	29	34.5	24.5	45.7	84	25	29.8	20.3	40.7
Dose 2	D-QIV	W/C	237	141	59.5	52.9	65.8	237	89	37.6	31.4	44.1	237	115	48.5	42	55.1
		Non- W/C	260	97	37.3	31.4	43.5	260	55	21.2	16.4	26.6	260	74	28.5	23.1	34.4
	FLUARIX	W/C	236	144	61	54.5	67.3	236	87	36.9	30.7	43.4	236	120	50.8	44.3	57.4
		Non- W/C	265	81	30.6	25.1	36.5	265	38	14.3	10.4	19.1	265	57	21.5	16.7	27
	TIV-2	W/C	236	141	59.7	53.2	66.1	236	86	36.4	30.3	42.9	236	116	49.2	42.6	55.7
		Non- W/C	266	99	37.2	31.4	43.3	266	58	21.8	17	27.3	266	73	27.4	22.2	33.2
	D-QIV-Y	W/C	181	128	70.7	63.5	77.2	181	98	54.1	46.6	61.6	181	88	48.6	41.1	56.1
		Non- W/C	81	35	43.2	32.2	54.7	81	29	35.8	25.4	47.2	81	15	18.5	10.8	28.7
Overall/dose	D-QIV	W/C	730	501	68.6	65.1	72	730	317	43.4	39.8	47.1	730	430	58.9	55.2	62.5
		Non- W/C	682	287	42.1	38.3	45.9	682	174	25.5	22.3	29	682	214	31.4	27.9	35
	FLUARIX	W/C	714	486	68.1	64.5	71.5	714	317	44.4	40.7	48.1	714	426	59.7	56	63.3
		Non- W/C	699	261	37.3	33.7	41	699	156	22.3	19.3	25.6	699	186	26.6	23.4	30.1
	TIV-2	W/C	722	505	69.9	66.5	73.3	722	316	43.8	40.1	47.5	722	419	58	54.3	61.7
		Non- W/C	691	266	38.5	34.9	42.2	691	152	22	19	25.3	691	202	29.2	25.9	32.8
	D-QIV-Y	W/C	374	274	73.3	68.5	77.7	374	208	55.6	50.4	60.7	374	192	51.3	46.1	56.5
		Non- W/C	165	76	46.1	38.3	54	165	58	35.2	27.9	43	165	40	24.2	17.9	31.5
Overall/subject	D-QIV	W/C	493	377	76.5	72.5	80.1	493	253	51.3	46.8	55.8	493	332	67.3	63	71.5
		Non- W/C	422	223	52.8	48	57.7	422	147	34.8	30.3	39.6	422	165	39.1	34.4	43.9
	FLUARIX	W/C	478	368	77	72.9	80.7	478	256	53.6	49	58.1	478	326	68.2	63.8	72.4
		Non- W/C	434	209	48.2	43.4	53	434	141	32.5	28.1	37.1	434	146	33.6	29.2	38.3
	TIV-2	W/C	486	383	78.8	74.9	82.4	486	261	53.7	49.2	58.2	486	322	66.3	61.9	70.5
		Non- W/C	425	199	46.8	42	51.7	425	130	30.6	26.2	35.2	425	153	36	31.4	40.8
	D-QIV-Y	W/C	193	162	83.9	78	88.8	193	134	69.4	62.4	75.8	193	121	62.7	55.5	69.5
		Non- W/C	84	54	64.3	53.1	74.4	84	44	52.4	41.2	63.4	84	29	34.5	24.5	45.7

TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV
W/C = White/Caucasian subjects, Non-W/C = Non-White/Caucasian subjects
For each dose and overall/subject:

- N= number of subjects with at least one administered dose
- n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

For overall/dose:

- N= number of administered doses

n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered

Table 114: Incidence and nature of grade 3 symptoms (solicited and unsolicited)

reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall by race (TVC)

			Any symptom					General symptoms					Local symptoms				
						95% CI					95% CI					95% CI	
	Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	D-QIV	White/Caucasian	493	43	8.7	6.4	11.6	493	25	5.1	3.3	7.4	493	22	4.5	2.8	6.7
		Non-White/Caucasian	422	10	2.4	1.1	4.3	422	6	1.4	0.5	3.1	422	5	1.2	0.4	2.7
	FLUARIX	White/Caucasian	478	36	7.5	5.3	10.3	478	21	4.4	2.7	6.6	478	20	4.2	2.6	6.4
		Non-White/Caucasian	434	14	3.2	1.8	5.4	434	8	1.8	0.8	3.6	434	7	1.6	0.7	3.3
	TIV-2	White/Caucasian	486	24	4.9	3.2	7.3	486	15	3.1	1.7	5.0	486	10	2.1	1.0	3.8
		Non-White/Caucasian	425	5	1.2	0.4	2.7	425	4	0.9	0.3	2.4	425	3	0.7	0.1	2.0
	D-QIV-Y	White/Caucasian	193	15	7.8	4.4	12.5	193	12	6.2	3.3	10.6	193	3	1.6	0.3	4.5
		Non-White/Caucasian	84	7	8.3	3.4	16.4	84	6	7.1	2.7	14.9	84	2	2.4	0.3	8.3
Dose 2	D-QIV	White/Caucasian	237	15	6.3	3.6	10.2	237	5	2.1	0.7	4.9	237	10	4.2	2.0	7.6
		Non-White/Caucasian	260	2	0.8	0.1	2.8	260	2	0.8	0.1	2.8	260	1	0.4	0.0	2.1
	FLUARIX	White/Caucasian	236	14	5.9	3.3	9.8	236	9	3.8	1.8	7.1	236	6	2.5	0.9	5.5
		Non-White/Caucasian	265	3	1.1	0.2	3.3	265	2	0.8	0.1	2.7	265	2	0.8	0.1	2.7
	TIV-2	White/Caucasian	236	8	3.4	1.5	6.6	236	4	1.7	0.5	4.3	236	5	2.1	0.7	4.9
		Non-White/Caucasian	266	5	1.9	0.6	4.3	266	3	1.1	0.2	3.3	266	2	0.8	0.1	2.7
	D-QIV-Y	White/Caucasian	181	14	7.7	4.3	12.6	181	13	7.2	3.9	12.0	181	1	0.6	0.0	3.0
		Non-White/Caucasian	81	6	7.4	2.8	15.4	81	6	7.4	2.8	15.4	81	0	0.0	0.0	4.5
Overall/dose	D-QIV	White/Caucasian	730	58	7.9	6.1	10.2	730	30	4.1	2.8	5.8	730	32	4.4	3.0	6.1
		Non-White/Caucasian	682	12	1.8	0.9	3.1	682	8	1.2	0.5	2.3	682	6	0.9	0.3	1.9
	FLUARIX	White/Caucasian	714	50	7.0	5.2	9.1	714	30	4.2	2.9	5.9	714	26	3.6	2.4	5.3
		Non-White/Caucasian	699	17	2.4	1.4	3.9	699	10	1.4	0.7	2.6	699	9	1.3	0.6	2.4
	TIV-2	White/Caucasian	722	32	4.4	3.1	6.2	722	19	2.6	1.6	4.1	722	15	2.1	1.2	3.4
		Non-White/Caucasian	691	10	1.4	0.7	2.6	691	7	1.0	0.4	2.1	691	5	0.7	0.2	1.7
	D-QIV-Y	White/Caucasian	374	29	7.8	5.3	10.9	374	25	6.7	4.4	9.7	374	4	1.1	0.3	2.7
		Non-White/Caucasian	165	13	7.9	4.3	13.1	165	12	7.3	3.8	12.4	165	2	1.2	0.1	4.3
Overall/subject	D-QIV	White/Caucasian	493	56	11.4	8.7	14.5	493	30	6.1	4.1	8.6	493	30	6.1	4.1	8.6
		Non-White/Caucasian	422	12	2.8	1.5	4.9	422	8	1.9	0.8	3.7	422	6	1.4	0.5	3.1
	FLUARIX	White/Caucasian	478	47	9.8	7.3	12.9	478	29	6.1	4.1	8.6	478	24	5.0	3.2	7.4
		Non-White/Caucasian	434	17	3.9	2.3	6.2	434	10	2.3	1.1	4.2	434	9	2.1	1.0	3.9
	TIV-2	White/Caucasian	486	32	6.6	4.5	9.2	486	19	3.9	2.4	6.0	486	15	3.1	1.7	5.0
		Non-White/Caucasian	425	10	2.4	1.1	4.3	425	7	1.6	0.7	3.4	425	5	1.2	0.4	2.7
	D-QIV-Y	White/Caucasian	193	26	13.5	9.0	19.1	193	22	11.4	7.3	16.7	193	4	2.1	0.6	5.2
		Non-White/Caucasian	84	10	11.9	5.9	20.8	84	9	10.7	5.0	19.4	84	2	2.4	0.3	8.3

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received Fluarix
TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV
For each dose and overall/subject:

- N= number of subjects with at least one administered dose
- n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

For overall/dose:

- N= number of administered doses
- n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered

Analysis by Region

The number and percentage of subjects who received the study vaccine dose by region is presented in table 115.

Table 115: Number and percentage of subjects who received study vaccine doses by region (TVC)

	D-QIV						FLUARIX						TIV-2						D-QIV-Y				Total					
	US N = 353		Europe N = 300		Asia N = 262		US N = 353		Europe N = 298		Asia N = 261		US N = 350		Europe N = 299		Asia N = 262		Europe N = 227		Asia N = 50		US N = 1056		Europe N = 1124		Asia N = 835	
Total number of doses received	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
1	186	52.7	148	49.3	84	32.1	186	52.7	145	48.7	80	30.7	182	52.0	144	48.2	83	31.7	15	6.6	0	0.0	554	52.5	452	40.2	247	29.6
2	167	47.3	152	50.7	178	67.9	167	47.3	153	51.3	181	69.3	168	48.0	155	51.8	179	68.3	212	93.4	50	100	502	47.5	672	59.8	588	70.4
Any	353	100	300	100	262	100	353	100	298	100	261	100	350	100	299	100	262	100	227	100	50	100	1056	100	1124	100	835	100

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received Fluarix,
TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV
US = Subjects from United States, Europe = Subjects from Germany, France and Czech Republic, Asia = Subjects from Philippines
N = number of subjects in each group or in total included in the considered cohort
n/% = number/percentage of subjects receiving the specified total number of doses
Any = number and percentage of subjects receiving at least one dose

Overall incidence and nature of solicited and unsolicited AEs (any grade and grade 3) during the 7-Day post-vaccination period analyzed by race (White/Caucasian versus Non-White/Caucasian) are presented in table 116 (any grade) and table 117 (grade 3).

Table 116: Incidence and nature of symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall by region (TVC)

			Any symptom					General symptoms					Local symptoms				
						95% CI					95% CI					95% CI	
	Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	D-QIV	US	353	228	64.6	59.4	69.6	353	137	38.8	33.7	44.1	353	195	55.2	49.9	60.5
		Europe	300	222	74.0	68.6	78.9	300	148	49.3	43.5	55.1	300	194	64.7	59.0	70.1
		Asia	262	100	38.2	32.3	44.3	262	62	23.7	18.7	29.3	262	66	25.2	20.1	30.9
	FLUARIX	US	353	222	62.9	57.6	67.9	353	143	40.5	35.3	45.8	353	188	53.3	47.9	58.6
		Europe	298	214	71.8	66.3	76.8	298	147	49.3	43.5	55.2	298	189	63.4	57.7	68.9
		Asia	261	86	33.0	27.3	39.0	261	58	22.2	17.3	27.8	261	58	22.2	17.3	27.8
	TIV-2	US	350	216	61.7	56.4	66.8	350	130	37.1	32.1	42.4	350	178	50.9	45.5	56.2
		Europe	299	231	77.3	72.1	81.9	299	152	50.8	45.0	56.6	299	191	63.9	58.2	69.3
		Asia	262	84	32.1	26.5	38.1	262	42	16.0	11.8	21.0	262	63	24.0	19.0	29.7
	D-QIV-Y	Europe	227	168	74.0	67.8	79.6	227	126	55.5	48.8	62.1	227	119	52.4	45.7	59.1
		Asia	50	19	38.0	24.7	52.8	50	13	26.0	14.6	40.3	50	10	20.0	10.0	33.7
Dose 2	D-QIV	US	167	80	47.9	40.1	55.8	167	44	26.3	19.8	33.7	167	64	38.3	30.9	46.2
		Europe	152	103	67.8	59.7	75.1	152	68	44.7	36.7	53.0	152	85	55.9	47.6	64.0
		Asia	178	55	30.9	24.2	38.2	178	32	18.0	12.6	24.4	178	40	22.5	16.6	29.3
	FLUARIX	US	167	76	45.5	37.8	53.4	167	46	27.5	20.9	35.0	167	61	36.5	29.2	44.3
		Europe	153	97	63.4	55.2	71.0	153	57	37.3	29.6	45.4	153	81	52.9	44.7	61.1
		Asia	181	52	28.7	22.3	35.9	181	22	12.2	7.8	17.8	181	35	19.3	13.9	25.9
	TIV-2	US	168	69	41.1	33.6	48.9	168	44	26.2	19.7	33.5	168	56	33.3	26.3	41.0
		Europe	155	105	67.7	59.8	75.0	155	65	41.9	34.1	50.1	155	86	55.5	47.3	63.5
		Asia	179	66	36.9	29.8	44.4	179	35	19.6	14.0	26.1	179	47	26.3	20.0	33.3
	D-QIV-Y	Europe	212	144	67.9	61.2	74.2	212	111	52.4	45.4	59.2	212	95	44.8	38.0	51.8
		Asia	50	19	38.0	24.7	52.8	50	16	32.0	19.5	46.7	50	8	16.0	7.2	29.1
Overall/dose	D-QIV	US	520	308	59.2	54.9	63.5	520	181	34.8	30.7	39.1	520	259	49.8	45.4	54.2
		Europe	452	325	71.9	67.5	76.0	452	216	47.8	43.1	52.5	452	279	61.7	57.1	66.2
		Asia	440	155	35.2	30.8	39.9	440	94	21.4	17.6	25.5	440	106	24.1	20.2	28.4
	FLUARIX	US	520	298	57.3	52.9	61.6	520	189	36.3	32.2	40.6	520	249	47.9	43.5	52.3
		Europe	451	311	69.0	64.5	73.2	451	204	45.2	40.6	50.0	451	270	59.9	55.2	64.4
		Asia	442	138	31.2	26.9	35.8	442	80	18.1	14.6	22.0	442	93	21.0	17.3	25.1
	TIV-2	US	518	285	55.0	50.6	59.4	518	174	33.6	29.5	37.8	518	234	45.2	40.8	49.6
		Europe	454	336	74.0	69.7	78.0	454	217	47.8	43.1	52.5	454	277	61.0	56.4	65.5
		Asia	441	150	34.0	29.6	38.6	441	77	17.5	14.0	21.3	441	110	24.9	21.0	29.3
	D-QIV-Y	Europe	439	312	71.1	66.6	75.3	439	237	54.0	49.2	58.7	439	214	48.7	44.0	53.5
		Asia	100	38	38.0	28.5	48.3	100	29	29.0	20.4	38.9	100	18	18.0	11.0	26.9
Overall/subject	D-QIV	US	353	241	68.3	63.1	73.1	353	151	42.8	37.6	48.1	353	206	58.4	53.0	63.6
		Europe	300	235	78.3	73.2	82.9	300	168	56.0	50.2	61.7	300	208	69.3	63.8	74.5
		Asia	262	124	47.3	41.2	53.6	262	81	30.9	25.4	36.9	262	83	31.7	26.1	37.7
	FLUARIX	US	353	234	66.3	61.1	71.2	353	156	44.2	38.9	49.5	353	195	55.2	49.9	60.5
		Europe	298	234	78.5	73.4	83.0	298	169	56.7	50.9	62.4	298	205	68.8	63.2	74.0
		Asia	261	109	41.8	35.7	48.0	261	72	27.6	22.3	33.4	261	72	27.6	22.3	33.4
	TIV-2	US	350	228	65.1	59.9	70.1	350	147	42.0	36.8	47.4	350	190	54.3	48.9	59.6
		Europe	299	244	81.6	76.7	85.8	299	177	59.2	53.4	64.8	299	204	68.2	62.6	73.5
		Asia	262	110	42.0	35.9	48.2	262	67	25.6	20.4	31.3	262	81	30.9	25.4	36.9
	D-QIV-Y	Europe	227	188	82.8	77.3	87.5	227	156	68.7	62.3	74.7	227	136	59.9	53.2	66.3
		Asia	50	28	56.0	41.3	70.0	50	22	44.0	30.0	58.7	50	14	28.0	16.2	42.5

US = Subjects from United States, Europe = Subjects from Germany, France and Czech Republic, Asia = Subjects from Philippines
For each dose and overall/subject:

- N= number of subjects with at least one administered dose
- n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

For overall/dose: N= number of administered doses

- n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered

Table 117: Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall by region (TVC)

			Any symptom					General symptoms					Local symptoms				
						95% CI					95% CI					95% CI	
	Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	D-QIV	US	353	22	6.2	3.9	9.3	353	10	2.8	1.4	5.1	353	13	3.7	2.0	6.2
		Europe	300	26	8.7	5.7	12.4	300	17	5.7	3.3	8.9	300	13	4.3	2.3	7.3
		Asia	262	5	1.9	0.6	4.4	262	4	1.5	0.4	3.9	262	1	0.4	0.0	2.1
	FLUARIX	US	353	17	4.8	2.8	7.6	353	8	2.3	1.0	4.4	353	9	2.5	1.2	4.8
		Europe	298	27	9.1	6.1	12.9	298	17	5.7	3.4	9.0	298	16	5.4	3.1	8.6
		Asia	261	6	2.3	0.8	4.9	261	4	1.5	0.4	3.9	261	2	0.8	0.1	2.7
	TIV-2	US	350	10	2.9	1.4	5.2	350	6	1.7	0.6	3.7	350	5	1.4	0.5	3.3
		Europe	299	18	6.0	3.6	9.3	299	12	4.0	2.1	6.9	299	8	2.7	1.2	5.2
		Asia	262	1	0.4	0.0	2.1	262	1	0.4	0.0	2.1	262	0	0.0	0.0	1.4
	D-QIV-Y	Europe	227	20	8.8	5.5	13.3	227	16	7.0	4.1	11.2	227	4	1.8	0.5	4.5
		Asia	50	2	4.0	0.5	13.7	50	2	4.0	0.5	13.7	50	1	2.0	0.1	10.6
Dose 2	D-QIV	US	167	8	4.8	2.1	9.2	167	4	2.4	0.7	6.0	167	4	2.4	0.7	6.0
		Europe	152	9	5.9	2.7	10.9	152	3	2.0	0.4	5.7	152	7	4.6	1.9	9.3
		Asia	178	0	0.0	0.0	2.1	178	0	0.0	0.0	2.1	178	0	0.0	0.0	2.1
	FLUARIX	US	167	9	5.4	2.5	10.0	167	6	3.6	1.3	7.7	167	5	3.0	1.0	6.8
		Europe	153	6	3.9	1.5	8.3	153	4	2.6	0.7	6.6	153	2	1.3	0.2	4.6
		Asia	181	2	1.1	0.1	3.9	181	1	0.6	0.0	3.0	181	1	0.6	0.0	3.0
	TIV-2	US	168	1	0.6	0.0	3.3	168	1	0.6	0.0	3.3	168	0	0.0	0.0	2.2
		Europe	155	8	5.2	2.3	9.9	155	4	2.6	0.7	6.5	155	5	3.2	1.1	7.4
		Asia	179	4	2.2	0.6	5.6	179	2	1.1	0.1	4.0	179	2	1.1	0.1	4.0
	D-QIV-Y	Europe	212	17	8.0	4.7	12.5	212	16	7.5	4.4	12.0	212	1	0.5	0.0	2.6
		Asia	50	3	6.0	1.3	16.5	50	3	6.0	1.3	16.5	50	0	0.0	0.0	7.1
Overall/dose	D-QIV	US	520	30	5.8	3.9	8.1	520	14	2.7	1.5	4.5	520	17	3.3	1.9	5.2
		Europe	452	35	7.7	5.5	10.6	452	20	4.4	2.7	6.8	452	20	4.4	2.7	6.8
		Asia	440	5	1.1	0.4	2.6	440	4	0.9	0.2	2.3	440	1	0.2	0.0	1.3
	FLUARIX	US	520	26	5.0	3.3	7.2	520	14	2.7	1.5	4.5	520	14	2.7	1.5	4.5
		Europe	451	33	7.3	5.1	10.1	451	21	4.7	2.9	7.0	451	18	4.0	2.4	6.2
		Asia	442	8	1.8	0.8	3.5	442	5	1.1	0.4	2.6	442	3	0.7	0.1	2.0
	TIV-2	US	518	11	2.1	1.1	3.8	518	7	1.4	0.5	2.8	518	5	1.0	0.3	2.2
		Europe	454	26	5.7	3.8	8.3	454	16	3.5	2.0	5.7	454	13	2.9	1.5	4.8
		Asia	441	5	1.1	0.4	2.6	441	3	0.7	0.1	2.0	441	2	0.5	0.1	1.6
	D-QIV-Y	Europe	439	37	8.4	6.0	11.4	439	32	7.3	5.0	10.1	439	5	1.1	0.4	2.6
		Asia	100	5	5.0	1.6	11.3	100	5	5.0	1.6	11.3	100	1	1.0	0.0	5.4
Overall/subject	D-QIV	US	353	29	8.2	5.6	11.6	353	14	4.0	2.2	6.6	353	16	4.5	2.6	7.3
		Europe	300	34	11.3	8.0	15.5	300	20	6.7	4.1	10.1	300	19	6.3	3.9	9.7
		Asia	262	5	1.9	0.6	4.4	262	4	1.5	0.4	3.9	262	1	0.4	0.0	2.1
	FLUARIX	US	353	24	6.8	4.4	9.9	353	14	4.0	2.2	6.6	353	12	3.4	1.8	5.9
		Europe	298	32	10.7	7.5	14.8	298	20	6.7	4.1	10.2	298	18	6.0	3.6	9.4
		Asia	261	8	3.1	1.3	5.9	261	5	1.9	0.6	4.4	261	3	1.1	0.2	3.3
	TIV-2	US	350	11	3.1	1.6	5.6	350	7	2.0	0.8	4.1	350	5	1.4	0.5	3.3
		Europe	299	26	8.7	5.8	12.5	299	16	5.4	3.1	8.5	299	13	4.3	2.3	7.3
		Asia	262	5	1.9	0.6	4.4	262	3	1.1	0.2	3.3	262	2	0.8	0.1	2.7
	D-QIV-Y	Europe	227	33	14.5	10.2	19.8	227	28	12.3	8.4	17.3	227	5	2.2	0.7	5.1
		Asia	50	3	6.0	1.3	16.5	50	3	6.0	1.3	16.5	50	1	2.0	0.1	10.6

D-QIV = Subjects of 3-17 years received D-QIV, FLUARIX = Subjects of 3-17 years received Fluarix,
TIV-2 = Subjects of 3-17 years received TIV-2, D-QIV-Y = Subjects of 6-35 months received D-QIV
US = Subjects from United States, Europe = Subjects from Germany, France and Czech Republic, Asia = Subjects from Philippines
For each dose and overall/subject:

- N= number of subjects with at least one administered dose
- n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

For overall/dose:

- N= number of administered doses
- n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered

3.2.4.7 Safety Conclusion

Reactogenicity:

For subjects 3 to 17 years old:

- Injection site pain was the most frequently reported solicited local AE in the three groups. Grade 3 local AE was reported for less than 2.3% of subjects.
- Drowsiness and irritability were the most frequently reported general AEs in the three treatment groups for subjects less than 6 years old. For this age population, grade 3 solicited general AEs, including fever, were reported for less than 1.7% of subjects.
- Fatigue, headache and muscle aches were the most frequently reported general AEs in the three groups for subjects from 6 to 17 years old. For this age population, grade 3 solicited general AEs, including fever, were reported for less than 1.5% of subjects.

For subjects 6 to 35 months old receiving D-QIV (D-QIV Young group):

- Injection site pain and redness were the most frequently reported local AEs. Grade 3 local AE was reported for less than 1.8% of subjects.
- Irritability was the most frequently reported general AE. The most frequently reported grade 3 general AE were fever (6.5%), loss of appetite (4.3%), irritability (4.0%) and drowsiness (2.5%).

Safety

For subjects 3 to 17 years old:

- 31.0% subjects from the D-QIV group, 33.4% from the Fluarix group and 33.8% from the TIV-2 group experienced at least one unsolicited AE during the 28-day post-vaccination period. Nasopharyngitis was the most frequently reported unsolicited AE. Grade 3 unsolicited AE were reported for less than 4.1% of subjects across the three groups.
- 0.9% subjects from the D-QIV group, 0.7% from the Fluarix group and 0.8% from the TIV-2 group experienced 12, 7 and 8 SAEs, respectively, during the entire study period, including one fatal SAE (car accident) for a subject of the Fluarix group. None of these SAEs were considered as related to vaccination.
- Two pIMDs were reported for two subjects from the TIV-2 group. None of these pIMDs was considered as related to vaccination.
- One pregnancy followed by an induced abortion was reported for a 17-year old subject from the Fluarix group.

For subjects 6 to 35 months old receiving D-QIV (D-QIV Young group):

- 60.3% subjects experienced at least one unsolicited AE during the 28-day post-vaccination period. Nasopharyngitis was the most frequently reported unsolicited AE. Grade 3 unsolicited AEs were reported for 7.2% of subjects.

- 1.5% subjects experienced 18 SAEs during the entire study period. None of these SAEs were considered as related to vaccination
- Two cases of febrile convulsion (16 and 98 days post-vaccination) were reported for two subjects from the D-QIV Young group (6-35 months old). None of these febrile convulsion cases were considered as related to vaccination.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

One of the co-primary objectives of study D-QIV-008 was to assess, for each strain, the consistency of the immune response among three lots of the D-QIV vaccine, according to pre-specified criteria described in Section 3.1 of this memo.

The clinical consistency of three different lots of the D-QIV vaccine was evaluated via the measurement of the HI immune response to the D-QIV vaccine in three groups of subjects, each receiving one of these lots.

The inferential analysis of consistency was based on the assessment of the equivalence of HI antibody GMTs among the three groups via pair-wise comparisons (lot 1 *versus* lot 2, lot 1 *versus* lot 3 and lot 2 *versus* lot 3).

All pair-wise GMTs were contained within the pre-specified [0.67, 1.5] interval, hence the consistency of the immunogenicity of three D-QIV vaccine lots was met.

The non-inferiority of the quadrivalent vaccine to trivalent vaccines containing the same A and B strains was established both in terms of HI antibody GMTs and of seroconversion rates using pre-specified statistical criteria in subjects 3 years of age and older (Study -008 and Study-003). The upper limits of the 95% CI on the GMT ratios (trivalent vaccine over quadrivalent vaccine) did not exceed the pre-defined limit of 1.5 for any of the four strains; and the upper limits of the 95%CI on the difference in seroconversion rates (trivalent vaccine minus quadrivalent vaccine) did not exceed the pre-defined limit of 10%.

For the B strain that is not included in the TIV vaccines, the superiority of the D-QIV vaccine to the trivalent vaccine lacking the B strain under consideration was established both in terms of HI antibody GMTs and of seroconversion rates using pre-specified statistical criteria in subjects 3 years of age and older (Study -008 and Study-003). The lower limit of the two-sided 95% CI on the GMT ratio (quadrivalent vaccine over trivalent vaccine) was greater than 1(a pre-specified criterion); and the lower limit of the two-sided 95% CI for the difference in seroconversion rate (quadrivalent vaccine minus trivalent vaccine) was greater than 0 (a pre-specified criterion).

The safety profile of the D-QIV vaccine has been established based on results obtained in a total of 4,631 D-QIV vaccine recipients including 1,490 children and 3,141 adults. Of these, 1,192 children (915 children 3-17 years of age, and 277 children 6-35 months of age) and 3,036 adults

(including 1,505 elderly subjects >64 years of age) participated in the two Phase III studies submitted within this BLA.

4.2 Conclusions and Recommendations

The data support the conclusion that, in subjects 3 years of age and older, the D-QIV candidate vaccine appears to provide non-inferior immunogenicity, compared to the licensed trivalent Fluarix vaccine, against four influenza strains.
Safety results have shown that the reactogenicity and safety profile of the D-QIV vaccine is similar to the profile of the licensed trivalent Fluarix vaccine and is also similar to the trivalent influenza vaccine (TIV-2) containing the B strain from the alternate lineage, in subjects above 3 years of age.

No safety concerns were raised based on the 6-months follow-up and no reported SAE was considered as vaccine-related.

Based on these findings it can be concluded that increasing the total antigen content by adding a fourth strain in the D-QIV vaccine does not appear to have a negative impact on the reactogenicity and safety profile relative to the trivalent Fluarix vaccine.

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