Application Type	BLA Supplement
STN	125408/127; 125408/127.2 received on 7/20/2015
CBER Received Date	April 23, 2015
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Division / Office	DVRPA/OVRR
Clinical Reviewer(s)	Ralph LeBlanc, M.D., Ph.D.
Project Manager	Helen S. Gemignani
Priority Review	No
Reviewer Name(s)	Lihan Yan, Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Tsai-Lien Lin, Ph.D., Team Leader A. Dale Horne, Dr. P.H., Branch Chief
Applicant	Novartis Vaccines and Diagnostics, Inc.
Established Name	Flucelvax® Quadrivalent, inactivated subunit-influenza vaccine
(Proposed) Trade Name	Flucelvax® Quadrivalent
Pharmacologic Class	Influenza Vaccine
Formulation(s), including Adjuvants, etc	Suspension for injection supplied in 0.5-mL single-dose pre-filled syringes.
Dosage Form(s) and Route(s) of Administration	H1N1-15 mcg;H3N2-15 mcg;B1-15 mcg; B2-15 mcg/0.5mL; Intramuscular (IM)
Dosing Regimen	One or two doses (at least 4 weeks apart) for persons 4 through 8 years of age depending on vaccination history; one dose for person 9 years of age and older
Indication(s) and Intended Population(s)	For use in persons 4 years of age or older for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

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GLOSSARY

AE	Adverse Event
ANCOVA	Analysis of Covariance
CBER	Center for Biologics Evaluation, Research and Review
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
ER	Emergency Room
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
HA	Hemagglutinin
HI	Hemagglutination Inhibition
ID	Identification
ILI	Influenza-like Illness
IM	Intramuscular
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MN	Microneutralization
NH	Northern Hemisphere
NOCD	New Onset of Chronic Disease
PPS	Per Protocol Set
QIV	Quadrivalent Influenza Vaccine
QIVc	Quadrivalent Cell-based Influenza Vaccine
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TIV	Trivalent Influenza Vaccine
TIVc	Trivalent Inactivated Cell-based Influenza Vaccine
TIV1c	Trivalent Inactivated Cell-based Influenza Vaccine containing one strain from B lineage (“B1” strain)
TIV2c	Trivalent Inactivated Cell-based Influenza Vaccine containing B strain from the alternate lineage (“B2” strain)
VSAE	Vaccine Serious Adverse Event
WHO	World Health Organization

1. EXECUTIVE SUMMARY

The applicant (Novartis Vaccines and Diagnostics, Inc.) submitted the supplemental Biologics License Application (sBLA) to pursue licensure of Flucelvax® Quadrivalent (QIVc) as a supplement to the existing Flucelvax® trivalent vaccine license, based on demonstration of noninferior immunogenicity and comparable safety with respect to Flucelvax® trivalent (TIVc). This supplement is intended to support the use of Flucelvax® Quadrivalent for use in the prevention of influenza in persons 4 years of age and older.

Included in this supplemental application are clinical data from studies V130_01 and V130_03 to demonstrate in the target populations a similar safety profile and noninferior immunogenicity of the vaccine compared to Flucelvax vaccine and to establish that the presence of a second B strain did not interfere with immune responses elicited by the other B strain or the two A strains. Study V130_01 was conducted among subjects 18 years and older, while Study V130_03 was conducted among subjects 4 through 17 years of age. In both studies, the primary immunogenicity objectives of noninferiority were met. There were no apparent safety concerns.

However, for the age group 4 through 17 years, the inferred effectiveness of QIVc depends on the approval of TIVc in this age group. Without the approval of TIVc in subjects 4 through 17 years of age, the conclusion regarding the inferred effectiveness of QIVc through demonstration of immunogenicity noninferiority to TIVc cannot be drawn.

2. CLINICAL AND REGULATORY BACKGROUND

The applicant's trivalent inactivated influenza vaccine (surface antigen, inactivated, cell-based), under the trade name Flucelvax (referred to as "TIVc" in this review), was approved for use in 2012 under the original BLA 125408. This vaccine is currently licensed for use in individuals 18 years of age and older. A supplemental BLA (sBLA) to extend the age indication for use in individuals 4 to < 18 years of age (children) has been submitted to the agency and was issued a complete response letter by the agency.

The applicant developed a quadrivalent version of TIVc, referred to as QIVc, to address the unmet medical need of better vaccine antigenic matching against co-circulating influenza B strains. The key difference from TIVc is the addition of a second B influenza strain that is included at a dose comparable to the other antigens, approximately 15 μg.

2.1 Disease or Health-Related Condition(s) Studied

Please refer to the clinical review.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Please refer to the clinical review.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

N/A

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

N/A

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

Submission quality is acceptable. The applicant has responded to all Agency information requests.

3.2 Compliance With Good Clinical Practices and Data Integrity

Please refer to the clinical and bioresearch and monitoring (BIMO) reviews.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

Please refer to the reviews of the corresponding discipline reviewers.

4.1 Chemistry, Manufacturing, and Controls

Please refer to the CMC review.

4.2 Assay Validation

Please refer to the assay review(s).

4.3 Nonclinical Pharmacology/Toxicology

N/A

4.4 Clinical Pharmacology

N/A

4.5 Clinical

Please refer to the clinical review.

4.6 Pharmacovigilance

Please refer to the pharmacovigilance review.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This review is based on two clinical studies, V130_01 and V130_03, submitted in the application. Each study is reviewed individually in separate subsections in Section 6. The review primarily focuses on the primary and key secondary immunogenicity objectives, as well as the safety objective.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

This review is based on the applicant's BLA supplement submission (STN 125408/127) dated April 23, 2015 and subsequent amendments to the submission, primarily Modules 2 and 5 in the following location in the Electronic Document Room (EDR):
(b) (4)

5.3 Table of Studies/Clinical Trials

There are two clinical trials conducted to support the application. A summary of these two studies is provided in Table 1.

Table 1: Summary of Clinical Studies

Study Number Year	Geographic Location (Numbers of Centers)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Patient
V130_01 2013-2014	US (40)	Safety and Immunogenicity of a Cell-based Quadrivalent Subunit Influenza Virus Vaccine and Cell- based Trivalent Subunit Influenza Virus Vaccines	Phase 3, Stratified, Randomized, Double-Blind, Multicenter, Non-Inferiority Study	QIVc; TIV1c; TIV2c 1 vaccination of 0.5 mL; IM dose	**Total:2680** 1335 676 669	Healthy subjects aged ≥18 years of age
V130_03 2013-2014	US (90)	Safety and Immunogenicity of a Cell-based Quadrivalent Subunit Influenza Virus Vaccine and Cell- based Trivalent Subunit Influenza Virus Vaccines	Phase 3, Stratified, Randomized, Double-Blind, Multicenter, Non-Inferiority Study	QIVc/TIV1c/TIV2c; 2 vaccinations of 0.5 mL, 4 weeks apart QIVc/TIV1c/TIV2c; 1 vaccination of 0.5 mL QIVc/TIV1c/TIV2c; 1 vaccination of 0.5 mL	**Total: 2333** 340/173/181 235/120/113 584/300/287	Healthy subjects Not previously vaccinated subjects ≥4 to to <9 years of age Previously vaccinated subjects ≥4 to to <9 years of age Previously vaccinated subjects 9 to < 18 yoa

Source: Synopses of Individual Studies submitted in the application.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: Study V130_01

Title of Study: A Phase III, Stratified, Randomized, Double-Blind, Multicenter, Noninferiority Study to Evaluate the Safety and Immunogenicity of a Cell-based Quadrivalent Subunit Influenza Virus Vaccine and Cell-based Trivalent Subunit Influenza Virus Vaccine in Adults ≥18 Years of Age.

6.1.1 Objectives (Primary, Secondary, etc.)

The primary Immunogenicity Objectives were:

- To demonstrate noninferiority of antibody responses to QIVc versus comparator TIVc in adults ≥18 years of age, as assessed by the ratio of geometric mean titer (GMT) at 3 weeks after vaccination (day 22) for each of the four vaccine strains.
- To demonstrate noninferiority of antibody responses to QIVc versus comparator TIVc 3 weeks after vaccination (day 22) in adults ≥18 years of age, as assessed by

differences in seroconversion rate for each of the four vaccine strains separately after vaccination.

The study was to be considered a success if both co-primary noninferiority objectives were achieved.

The key secondary immunogenicity objective was:

- To evaluate the antibody responses to all 4 influenza vaccine strains after vaccination in 2 age cohorts: ≥18 years to <65 years of age and ≥65 years of age, according to the Center for Biologics Evaluation and Research, and CBER review criteria as defined for the different age-cohorts.

The safety objective was:

- To evaluate the safety and tolerability of QIVc, TIV1c, and TIV2c in adults ≥18 years of age.

6.1.2 Design Overview

This was a phase 3, randomized, double-blind, multicenter, noninferiority study to assess the safety and immunogenicity of QIVc, TIV1c, and TIV2c in subjects ≥18 years of age. Approximately 2680 subjects ≥18 years of age were enrolled in a 1:1 stratified fashion into two age cohorts: subjects ≥18 to <65 and ≥ 65 years of age. Subjects were randomized 2:1:1 to receive QIVc, TIV1c, or TIV2c. All subjects were to be evaluated for safety and immunogenicity. The study was conducted between November 14, 2013 and July 11, 2014.

6.1.3 Population

Healthy subjects 18 years of age and older were enrolled in the study.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The doses selected in the study are standard influenza vaccine doses containing approximately 15 μg of HA of each of the strains of influenza virus, as recommended by the WHO for quadrivalent/trivalent vaccines for the 2013/2014 influenza season (Table 2).

Table 2: Vaccine Formulations

Vaccine	**Lot No, Expiration Date**	**Strains recommended by WHO for the 2013/2014 influenza season**
QIVc	Lot No. 005011 June 30, 2014	A/Brisbane/10/2010 [H1N1], A/Texas/50/2012 NYMC X-223A [H3N2], B/Massachusetts/2/2012 [B1], B/Brisbane/60/2008 [B2]
TIV1c	Lot No. 004011 June 30, 2014	A/Brisbane/10/2010 [H1N1], A/Texas/50/2012 NYMC X-223A [H3N2], B/Massachusetts/02/2012 [B1]
TIV2c	Lot No. 003011 June 30, 2014	A/Brisbane/10/2010 [H1N1], A/Texas/50/2012 NYMC X-223A [H3N2], B/Brisbane/60/2008 [B2]

Source: Reviewer summary based on information on Page 72 of the CSR for Study V130_01.

After randomization on Day 1, all subjects were to receive a dose of approximately 0.5mL study vaccine administered (IM) in the deltoid muscle, preferably of the non-dominant arm.

6.1.6 Sites and Centers

The study was conducted in 40 centers in the USA.

6.1.7 Surveillance/Monitoring

Please refer to the clinical review.

6.1.8 Endpoints and Criteria for Study Success

The primary and key secondary immunogenicity endpoints were:

- GMT of all 4 influenza strains as measured on day 1, day 22.
- Ratio of GMTs as calculated at day 22:
    a. A/H1N1: TIV1c/QIVc
    b. A/H3N2: TIV1c/QIVc
    c. B1: TIV1c/QIVc
    d. B2: TIV2c/QIVc.
- Percentages of subjects achieving seroconversion and HI ≥1:40 as calculated for all 4 influenza strains at day 1 and day 22.
- Differences in percentages of subjects achieving seroconversion as calculated at day 22:
    a. A/H1N1: TIV1c-QIVc
    b. A/H3N2: TIV1c-QIVc
    c. B1: TIV1c-QIVc
    d. B2: TIV2c- QIVc.

Seroconversion was defined as post-vaccination HI titer ≥1:40 in subjects seronegative at baseline (i.e., HI titer <1:10 at Day 1), and as a minimum of 4-fold increase in post-vaccination HI titer in subjects seropositive at baseline (i.e., HI titer ≥1:10 at Day 1). The primary analysis was based on noninferiority tests for all subjects pooled from two age cohorts. The noninferiority margins were 1.5 fold for the GMT ratio and 10% for the difference in percentages of subjects achieving seroconversion.

Percentages of subjects achieving seroconversion and HI ≥1:40 as calculated for all four influenza strains at post-vaccination were evaluated according to CBER criteria. Specifically,

1) The thresholds for the seroconversion rates are at least 40% and 30% for subjects 18-64 years of age and subjects ≥65 years of age, respectively; and
2) The thresholds for the percentages of subjects with HI ≥1:40 are at least 70% and 60% for subjects 18-64 years of age and subjects ≥65 years of age, respectively.

The measures for assessing safety and tolerability were as follows:

- Percentages of subjects with solicited local and systemic AEs and other solicited data as measured for 7 days following vaccination and calculated for 4 time

intervals after vaccination: 30 minutes, day 1 through day 3 (with and without 30 minutes), day 4 through day 7 (with and without 30 minutes), day 1 through day 7 (with and without 30 minutes).

- Percentages of subjects with any unsolicited AEs reported were assessed from day 1 through day 22.
- Percentages of subjects reporting SAEs, medically attended AEs, AEs leading to withdrawal from the study, new onset of chronic diseases (NOCDs), and concomitant medications associated with these events as collected from day 1 through day 181.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis Populations

The following analysis populations were considered:

- Full Analysis Set (FAS) included all subjects who received a study vaccination. FAS immunogenicity set included these subjects who provided immunogenicity data at Visit 1 and Visit 2. FAS populations were to be analyzed "as randomized."
- Per Protocol Set (PPS) included all subjects in the FAS set who correctly received the vaccine and had no major protocol deviations such as withdrawal of informed consent, experiencing ILI- and RT-PCR-confirmed influenza during the treatment period.
- Safety Set included all subjects who provided relevant safety data. The safety set population was analyzed "as treated."

Analysis of Primary Objectives

The primary noninferiority testing was conducted on the pooled age cohorts (subjects ≥18 years of age) using the day 22 HI titers and the PPS.

For GMT comparison, HI antibody titers were logarithmically (base$_{10}$) transformed and modeled as shown below, using analysis of covariance (ANCOVA) with a qualitative factor for vaccine group ($\alpha_{ik,}$ i = QIVc, TIVc1, TIVc2), center ($\delta_{lk,}$ l=1), age group (γ_{mk}, m= 18-64, ≥ 65), and a common slope (β) representing the impact of the log-prevaccination antibody titer x_{ik}:

$$\mu_{ik} = \lambda_k + \alpha_{ik} + \delta_{lk} + \gamma_{mk} + \beta x_{ik} \text{ (k=strain: 1, 2, 3, 4).}$$

The adjusted GMTs, adjusted ratios of geometric means and corresponding 2-sided confidence intervals (CIs) were calculated based on these models. The success criterion for GMT comparisons was that the upper bound of the two-sided 95% confidence interval (CI) for the ratio of GMTs ($GMT_{TIV1c \text{ or } TIV2c}$ /GMT_{QIVc}) for HI antibody should not exceed the noninferiority margin of 1.5.

For seroconversion rate comparison, the vaccine group difference (seroconversion comparator TIVc – seroconversion QIVc) in the percentage of subjects achieving seroconversion was calculated using a binomial distribution. The two-sided 95% CIs were constructed using the Mettinen and Nurminen method.

The success criterion for seroconversion rate comparisons was that the upper bound of the two-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV1c or TIV2c - %seroconversion QIVc) for HI antibody should not exceed the margin of 10%.

The study was to be considered a success if both co-primary noninferiority objectives are achieved in the pooled age cohort.

Analysis of Key Secondary Objectives

The numbers and percentages of subjects achieving seroconversion and percentages of subjects achieving an HI titer ≥1:40, with point estimates and two-sided 95% CIs, were computed using the Clopper-Pearson method for each strain and age cohort. The lower bounds of the 95% CIs were to be compared to the corresponding threshold described in the CBER criteria.

Analysis of Safety Objectives

Safety endpoints were analyzed in a descriptive manner.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics

Demographic characteristics were well balanced among the QIVc, TIV1c, and TIV2c groups (Table 3). Across the groups, the mean age of subjects was about 57 years; weight about 86 to 87 kg, and height about 169 cm among the groups. The majority of the enrolled subjects were Caucasians, 75.6% to 78.5% across groups. Overall, a higher percentage of females (54.8% to 58.6%) as compared to males (41.4% to 45.2%) were enrolled. The demographic characteristics of the FAS and PPS were similar to those of the enrolled sets (results are not presented.)

Table 3: Demographic Characteristics - All Enrolled Set

	QIVc (N=1335)	TIV1c (N=676)	TIV2c (N=669)
Age (years)±SD	57.4±17.8	57.2±18.0	57.1±18.1
18-64 years	674 (50.5%)	334 (49.4)	332 (49.6)
65 years and older	661 (49.5%)	342 (50.5)	337 (50.4)
Sex			
Male	603 (45.2%)	284 (42.0%)	277 (41.4%)
Female	732 (54.8%)	392 (58.0%)	392 (58.6%)
Height (cm) ±SD	169.4±9.9	168.8±10.3	168.6±10.1
Weight (kg) ±SD	86.9±22.7	86.2±21.3	85.8±22.1
Body Mass Index (kg/m^2)±SD	30.2±7.3	30.2±6.7	30.2±7.4
Race/Ethnicity			
Asian	4 (0.3%)	3 (0.4%)	3 (0.4%)
American Indian	10 (0.7%)	7 (1.0%)	2 (0.3%)
Black	179 (13.4%)	80 (11.8%)	81 (12.1%)
Native Hawaiian	2 (0.1%)	2 (0.3%)	0 (0.0%)
Hispanic	122 (9.1%)	59 (8.7%)	53 (7.9%)
Caucasians	1009 (75.6%)	519 (76.8%)	525 (78.5%)
Other	9 (0.7%)	6 (0.9%)	5 (0.7%)

*Source: Adapted from Figure 10.1-1 and Table 11.2-1; Clinical Study Report V130_*01

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Healthy male and female subjects ≥18 years of age at the time of enrollment who had not been exposed to influenza (either through expected influenza illness or influenza vaccination) within the past 6 months and who had no contraindications to influenza vaccine were to be enrolled.

6.1.10.1.3 Subject Disposition

A total of 2680 subjects were enrolled into the study. Of these, 1335 subjects were in the QIVc group, 676 subjects in the TIV1c group, and 669 subjects in the TIV2c group. A summary of the subject disposition is provided in Table 4.

Of the 2680 enrolled subjects, 2585 (96.5%) completed the study. A total of 95 (3.5%) subjects prematurely withdrew from the study. Across the groups, the most common reason for premature withdrawal was loss to follow-up for 48 (1.8%) subjects. A total of 143 (5.3%) subjects had major protocol deviations in the study. The most common major protocol deviation across all the groups was noncompliance with blood draw schedules in 99 (3.7%) subjects. The FAS and PPS populations consisted of 98.4% and 95.5% of the enrolled subjects, respectively.

Table 4: Disposition of Subjects in Study V130_01

Vaccine Group	QIVc Number (%) of subjects	TIV1c Number (%) of subjects	TIV2c Number (%) of subjects
Enrolled (N)	1335	676	669
Completed protocol	1285 (96.3)	652 (96.4)	648 (96.9)
Premature withdrawals	50 (3.7)	24 (3.6)	21 (3.1)
Withdrawal due to AE	1 (0.1)	0 (0.0)	0 (0.0)
Death	5 (0.4)	5 (0.7)	2 (0.3)
Withdrawal by subject	7 (0.5)	3 (0.4)	4 (0.6)
Lost to follow-up	26 (1.9)	9 (1.3)	13 (1.9)
Administrative reasons	6 (0.4)	7 (1)	1 (0.1)
Protocol deviations	1 (0.1)	0 (0.0)	1 (0.1)
Other	4 (0.3)	0 (0.0)	0 (0.0)
Safety Set	**1324 (99.2)**	**673 (99.6)**	**665 (99.4)**
Subjects with at least one major protocol deviation	79 (5.9)	38 (5.6)	26 (3.9)
Full Analysis Set (FAS)	**1311 (98.2)**	**664 (98.2)**	**658 (98.4)**
Per Protocol Set (PPS)	**1250 (93.6)**	**635 (93.9)**	**639 (95.5)**

*Source: Adapted from Tables 10.1-1, 10.2-1, and 11.1-1; Clinical Study Report V130_*01

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The analysis results for the primary endpoints are presented in Table 5 for the post-vaccination GMT comparisons and in Table 6 for the comparisons of seroconversion rates. The results were compared between the QIVc and TIV1c groups for the H1N1, H3N2, and B1 strains, while they were compared between the QIVc and TIV2c groups for the B2 strain. For all four strains, the upper bounds of the two-sided 95% CIs for the ratios of GMTs ($GMT_{T\ IV1c\ or\ T\ IV2c}$ /GMT_{QIVc}) for HI antibody remained within the noninferiority margin of 1.5 (1.1 for A/H1N1, 1.1 for A/H3N2, 1.0 for B1, and 1.0 for B2). For all four influenza strains, the upper bounds of the 2-sided 95% CIs on the differences between the seroconversion rates (%seroconversion TIV1c or TIV2c – % seroconversion QIVc) for HI antibody also remained within the noninferiority margin of 10% (4.2% for A/H1N1, 1.9% for A/H3N2, 2.8% for B1, and 0.2% for B2). Therefore, the primary objectives were met.

Table 5: Primary Analysis of Ratios of HI Geometric Mean Titers 3 Weeks after the Vaccination - Per Protocol Set

Strain	QIVc (N=1250) GMT	TIV1c (N=635) or TIV2c (N=639)* GMT	GMT Ratio (95% CI)
H1N1	302.8	298.9	1.0 (0.9, 1.1)
H3N2	372.3	378.4	1.0 (0.9, 1.1)
B1	133.2	115.6	0.9 (0.8, 1.0)
B2	177.2	164.0	0.9 (0.9, 1.0)

*For H1N1, H3N2, and B1 strains, the ratios of GMTs were calculated as TIV1c/QIVc, while for the B2 strain the ratio of GMTs was calculated as TIV2c/QIVc.
Source: Adapted from Table 11.4.1-1; Clinical Study Report V130_01.

Table 6: Primary Analysis of Seroconversion Rates at 3 Weeks after the Vaccination - Per Protocol Set

Strain	QIVc (N=1250) n (%)	TIV1c (N=635) or TIV2c (N=639)* n (%)	Difference (95% CI)
H1N1	615 (49.2%)	309 (48.7%)	-0.5% (-5.3%, 4.2%)
H3N2	479 (38.3%)	226 (35.6%)	-2.7% (-7.2%, 1.9%)
B1	457 (36.6%)	221 (34.8%)	-1.8% (-6.2%, 2.8%)
B2	497 (39.8%)	226 (35.4%)	-4.4% (-8.9%, 0.2%)

*For H1N1, H3N2, and B1 strains, differences in seroconversion rate were calculated as TIV1c - QIVc, while for the B2 strain difference in seroconversion rate was calculated as TIV2c - QIVc.
Source: Adapted from Table 11.4.1-2; Clinical Study Report V130_01.

Reviewer's comment: The applicant made a typo in the footnote of Table 11.4.1-2, describing that the differences in seroconversion were calculated as "TIV1c (or TIV2c)/QIVc," rather than as the arithmetic difference, i.e., TIV1c (TIV2c) – QIVc.

6.1.11.2 Analyses of Secondary Endpoints

Table 7 presents the results for the analysis of the key secondary endpoints for the PPS population in the QIVc group, separately for age groups 18-64 years and ≥65 years. Both CBER immunogenicity criteria for seroconversion and HI titer ≥1:40 were met for A/H1N1, A/H3N2, B1, and B2 influenza strains for subjects 18 through 64 years of age. However, for subjects ≥65 years of age, both CBER immunogenicity criteria for seroconversion and HI titer ≥1:40 were met for the A/H1N1influenza strain. For the A/H3N2, B1, and B2 influenza strains, while the CBER immunogenicity criteria for HI titer ≥1:40 were met, the criteria for seroconversion were not met.

The above conclusions were the same for the corresponding TIV1c/TIV2c group.

Table 7: Analysis of Post-vaccination Results in the QIVc Group According to CBER Criteria – Per Protocol Set

Parameter	**# (%) of subjects seroconverted (95% CI)**	**# (%) of subjects seroconverted (95% CI)**	**# (%) of subjects with HI titer ≥1:40 (95% CI)**	**# (%) of subjects with HI titer ≥1:40 (95% CI)**
Age Group	**18-64 yrs (N=629)**	**≥65 yrs (N=621)**	**18-64 yrs (N=629)**	**≥65 yrs (N=621)**
H1N1	398 (63.3%) (59.4%, 67.1%)	218 (35.1%) (31.3%, 39.0%)	620 (98.6%) (97.3%, 99.3%)	584 (94.0%) (91.9%, 95.8%)
H3N2	309 (49.1%) (45.2%, 53.1%)	170 (27.4%) (23.9%, 31.1%)	620 (98.6) (97.3%, 99.3%)	610 (98.2%) (96.9%, 99.1%)
B1	327(52.0%) (48.0%, 56.0%)	130 (20.9%) (17.8%, 24.3%)	600 (95.4%) (93.4%, 96.9%)	570 (91.8%) (89.3%, 93.8%)
B2	330(52.5%) (48.5%, 56.4%)	167 (26.9%) (23.4%, 30.6%)	623 (99.0%) (97.9%, 99.6%)	598 (96.3%) (94.5%, 97.6%)

Source: Reviewer's analysis.

Reviewer's comment: In Tables 11.4.1-4 and 11.4.1-5 of the Clinical Study Report, the applicant presented analysis results for the Full Analysis Set (FAS, including subjects with major violations and with analysis as randomized), corresponding to the PPS analyses whose results are shown in Table 7. The results are similar to those presented in Table 7, and lead to the same conclusions.

6.1.11.3 Subpopulation Analyses

Please see section 7.

6.1.11.4 Dropouts and/or Discontinuations

The dropout rate in the study is low. It is unlikely that the missing data would have a notable, qualitative effect on the study conclusions.

6.1.11.5 Exploratory and Post Hoc Analyses

N/A

6.1.12 Safety Analyses

Solicited local and systemic AEs were reported from Day 1 through Day 7. All unsolicited AEs were collected from day 1 through day 22 after vaccination. All SAEs, medically attended AEs, AEs leading to withdrawal from the study, and NOCDs were collected from day 1 through day 181.

Solicited Adverse Events

As shown in Table 8, the percentages of subjects in the QIVc, TIV1c, and TIV2c groups who reported solicited local AEs were 41.8%, 35.8%, and 36.5%, respectively, and 28.5%, 28.7%, and 29.3% of subjects reported solicited systemic AEs. respectively. The percentages of subjects reporting solicited local AEs were higher in the QIVc group than

in the TIV1c and TIV2c groups, although the percentages of subjects reporting solicited systemic AEs were similar across the three vaccine groups.

Table 8: Number (%) of Subjects with at Least One Solicited Adverse Events from Day 1 through Day 7 after Vaccination- Solicited Safety Set

	≥18 years			≥18 to <65 years			≥65 years		
	QIVc	**TIV1c**	**TIV2c**	**QIVc**	**TIV1c**	**TIV2c**	**QIVc**	**TIV1c**	**TIV2c**
	N=1319	N=670	N=663	N=663	N=330	N=327	N=656	N=340	N=336
Any	681 (51.6%)	320 (47.8%)	340 (51.3%)	410 (61.8%)	187 (56.7%)	195 (59.6%)	271 (41.3%)	133 (39.1%)	145 (43.2%)
Local	551 (41.8%)	240 (35.8%)	242 (36.5%)	343 (51.7%)	146 (44.2%)	149 (45.6%)	208 (31.7%)	94 (27.6%)	93 (27.7%)
Systemic	376 (28.5%)	192 (28.7%)	194 (29.3%)	239 (36.0%)	118 (35.8%)	119 (36.4%)	137 (20.9%)	74 (21.8%)	75 (22.3%)
Others[a]	66 (5.0%)	20 (3.0%)	30 (4.5%)	36 (5.4%)	12 (3.6%)	11 (3.4%)	30 (4.6%)	8 (2.4%)	19 (5.7%)

[a] *Others* refers to other indicators of reactogenicity, use of analgesic/antipyretic medications for prophylaxis, and /or treatment and body temperature.
Source: Table 12.2.1-1; Clinical Study Report V130_01.

Unsolicited Adverse Events

As shown in Table 10, from day 1 through day 22, the percentages of subjects in the QIVc, TIV1c, and TIV2c groups who reported unsolicited AEs were similar (16.1%, 14.7%, and 16.5%, respectively). The percentages of AEs judged by the investigator as possibly related to the study vaccine were also similar across the groups (3.9%, 3.1%, and 4.2%, respectively).

Table 9: Number (%) of Subjects ≥18 Years of Age with Unsolicited Adverse Events After Vaccination- Unsolicited Safety Set

	QIVc (N=1324)	**TIV1c (N=673)**	**TIV2c (N=665)**
Any AE	213 (16.1%)	99 (14.7%)	110 (16.5%)
Possibly related AE	52 (3.9%)	21 (3.1%)	28 (4.2%)
SAE	52 (3.9%)	22 (3.3%)	21 (3.2%)
Possibly related SAE	0 (0.0%)	0 (0.0%)	0 (0.0%)
AE leading to premature withdrawal from the study	2 (0.2%)	1 (0.1%)	1 (0.2%)
Medically attended AE	344 (26.0%)	172 (25.6%)	166 (25.0%)
NOCD	62 (4.7%)	25 (3.7%)	29 (4.4%)
Death	5 (0.4%)	5 (0.7%)	2 (0.3%)

Source: Table 12.2.1-2; Clinical Study Report V130_01.

6.1.12.1 Methods

Please refer to the clinical review.

6.1.12.3 Deaths

Twelve subjects died during this study (5 [0.4%] subjects from the QIVc group, 5 [0.7%] from the TIV1c group, and 2 [0.3%] from the TIV2c group). Investigators did not consider any of these events to be related to the vaccine.

6.1.12.4 Nonfatal Serious Adverse Events

Overall, 95 subjects experienced SAEs (52 [3.9%] subjects in the QIVc, 22 [3.3%] in the TIV1c, and 21 [3.2%] in the TIV2c groups). The respective investigators judged all the SAEs to be unrelated to the study vaccine. Most of the SAEs experienced throughout the study period were consistent with common illnesses or infections that occur in adults and the elderly. Please refer to the clinical review for more details and clinical significance of the observed events.

6.1.12.5 Adverse Events of Special Interest (AESI)

Table 10 displays the number of subjects ≥18 to <65 years of age and ≥65 years of age with unsolicited adverse events of ≥1% from day 1 through day 181. The percentages of subjects in the QIVc, TIV1c, and TIV2c groups who reported unsolicited AEs from day 1 through day 181 after vaccination were 42.8%, 45.2%, and 42.7%, respectively. The percentages of AEs judged by the investigator as possibly related to the study vaccine were similar across the groups (4.4%, 3.8%, and 4.5%, respectively). Most of the unsolicited AEs were mild to moderate in severity. The majority of unsolicited AEs were regarded as resolved or stabilized at the time of study termination.

Table 10: Number (%) of Subjects ≥18 to <65 Years of Age and ≥65 Years of Age with Unsolicited Adverse Events by Preferred Term (≥1%) From Day 1 Through Day 181 - Unsolicited Safety Set

	≥18 to <65 years			≥65 years		
Vaccine Group	**QIVc**	**TIV1c**	**TIV2c**	**QIVc**	**TIV1c**	**TIV2c**
	N=665	N=330	N=328	N=659	N=342	N=337
Upper respiratory tract infection	23 (3.5%)	9 (2.7%)	15 (4.6%)	22 (3.3%)	12 (3.5%)	11 (3.3%)
Nasopharyngitis	20 (3.0%)	8 (2.4%)	9 (2.7%)	29 (4.4%)	14 (4.1%)	11 (3.3%)
Sinusitis	16 (2.4%)	10 (3.0%)	9 (2.7%)	10 (1.5%)	11 (3.2%)	9 (2.7%)
cough	8 (1.2%)	7 (2.1%)	6 (1.8%)	14 (2.1%)	17 (5.0%)	11 (3.3%)
Influenza-like illness	13 (2.0%)	3 (0.9%)	6 (1.8%)	-	-	-
Oropharyngeal pain	10 (1.5%)	5 (1.5%)	5 (1.5%)	8 (1.2%)	6 (1.7%)	5 (1.5%)
Bronchitis	12 (1.8%)	5 (1.5%)	2 (0.6%)	19 (2.9%)	5 (1.5%)	4 (1.2%)
Headache	12 (1.8%)	1 (0.3%)	5 (1.5%)	4 (0.6%)	6 (1.7%)	5 (1.5%)
Diarrhoea	10 (1.5%)	4 (1.2%)	3 (0.9%)	7 (1.1%)	9 (2.6%)	4 (1.2%)
Hypertension	5 (0.8%)	3 (0.9%)	6 (1.8%)	7 (1.1%)	4 (1.2%)	3 (0.9%)
Urinary tract infection	11 (1.7%)	2 (0.6%)	1 (0.3%)	15 (2.3%)	6 (1.7%)	5 (1.5%)
Arthralgia	-	-	-	9 (1.4%)	12 (3.5%)	5 (1.5%)
Rhinorrhoea	-	-	-	7 (1.1%)	9 (2.6%)	7 (2.1%)
Back pain	-	-	-	9 (1.4%)	6 (1.7%)	3 (0.9%)
Fatigue	-	-	-	7 (1.1%)	7 (2.0%)	3 (0.9%)
Nasal congestion	-	-	-	7 (1.1%)	6 (1.7%)	4 (1.2%)

Source: Table 12.2.1-1; Clinical Study Report V130_01.

6.1.12.6 Clinical Test Results

Please refer to the clinical review.

6.1.12.7 Dropouts and/or Discontinuations

One subject from the QIVc group withdrew from the study primarily due to an AE (acute myeloid leukemia and worsening of diabetes). The investigator assessed these events as being unrelated to the study vaccine.

6.1.12.8 Safety Subgroup Analyses

Table 11 presents the summary of unsolicited AEs by sex. The overall AE rates appeared to be slightly higher in females than in males with the differences ranging between 2% to 7%. AE rates were similar across the vaccine groups within each sex group.

Table 12 presents the summary of unsolicited AEs by race/ethnicity origin. The overall AE rate appeared to be slightly higher among Caucasians than among Blacks and Hispanics. The rates in the other categories were similar across the racial groups.

Table 11: Unsolicited Adverse Events in Subjects 18 Years of Age and Older by Sex – Unsolicited Safety Set

	Female	Female	Female	Male	Male	Male
n (%)	**QIVc (N = 391)**	**TIV1c (N = 596)**	**TIV2c (N=391)**	**QIVc (N = 596)**	**TIV1c (N = 281)**	**TIV2c (N=274)**
Any AE	294 (40.4)	167 (42.6)	151 (38.6)	200 (33.6)	76 (27.0)	100 (36.5)
Possibly/probably related AE	38 (5.2)	19 (4.8)	19 (4.9)	19 (3.2)	3 (1.1)	11 (4.0)
Any SAE	26 (3.6)	15 (3.8)	6 (1.5)	26 (4.4)	7 (2.5)	15 (5.5)
Possibly/probably related SAE	0	0	0	0	0	0
AEs leading to premature withdrawal	0	0	0	1	0	0
Medically attended AE	207 (28.4)	118 (30.1)	100 (25.6)	137 (23.0)	54 (19.2)	66 (24.1)
NOCD	29 (4.0)	16 (4.1)	18 (4.6)	33 (5.5)	9 (3.2)	11 (4.0)
Deaths	1	3	0	4	2	2

Source: CSR V130_01: Table 14.3.1.13.6, Table 14.3.1.18.6, Table 14.3.2.2.5, Table 14.3.2.3.5, Table 14.3.2.11, Table 14.3.2.5.6, Table 14.3.2.6.6, Listing 16.2.7.2

Table 12: Unsolicited Adverse Events in Subjects 18 Years of Age and Older by Race/Ethnicity – Unsolicited Safety Set

	Black	Black	Black	Caucasian	Caucasian	Caucasian	Hispanic	Hispanic	Hispanic
n (%)	**QIVc (N =175)**	**TIV1c (N = 77)**	**TIV2c (N=80)**	**QIVc (N = 1005)**	**TIV1c (N =519)**	**TIV2c (N=523)**	**QIVc (N = 120)**	**TIV1c (N =59)**	**TIV2c (N=52)**
Any AE	45 (25.7)	19 (24.7)	24 (30.0)	412 (41.0)	210 (40.5)	210 (40.2)	30 (25.0)	12 (20.3)	10 (19.2)
Possibly/probably related AE	6 (3.4)	2 (2.6)	5 (6.3)	43 (4 3)	19 (3.7)	24 (4.6)	5 (4.2)	1 (1.7)	1 (1.9)
Any SAE	5 (2.9)	2 (2.6)	3 (3.8)	44 (4.4)	20 (3.9)	17 (3 3)	3 (2.5)	0	1 (1.9)
Possibly/probably related SAE	0	0	0	0	0	0	0	0	0
AEs leading to premature withdrawal	0	0	0	1 (0.1)	0	0	0	0	0
Medically attended AE	25 (14.3)	12 (15.6)	10 (12.5)	293 (29.2)	153 (29.5)	143 (27.3)	21 (17.5)	5 (8.5)	7 (13.5)
NOCD	7 (4.0)	2 (2.6)	3 (3.8)	51 (5 1)	22 (4.2)	24 (4.6)	3 (2.5)	1 (1.7)	2 (3.8)
Deaths	0	0	1	5	5	1	0	0	0

Source: CSR V130_01: Table 14.3.1.13.7, Table 14.3.1.18.7, Table 14.3.2.3.6, Table 14.3.2.11, Table 14.3.2.5.7, Table 14.3.2.6.7, Listing 16.2.4.1.

6.2 Trial #2: V130_03

Title of Study: "A Phase III, Stratified, Randomized, Double-Blind, Multicenter, Noninferiority Study to Evaluate Safety and Immunogenicity of Cell-Based Quadrivalent Subunit Influenza Virus Vaccine and Cell-Based Trivalent Subunit Influenza Virus Vaccines in Subjects of Ages ≥4 Years to <18 Years"

6.2.1 Objectives (Primary, Secondary, etc.)

The study objectives are described as follows:

Primary Immunogenicity Objectives:

- To demonstrate noninferiority of antibody responses to QIVc compared to TIVc in subjects ≥4 to <18 years of age, as assessed by the ratio of geometric mean titers (GMT) for each of the four vaccine strains separately after vaccination.
- To demonstrate noninferiority of antibody responses to QIVc compared to TIVc after vaccination in subjects ≥4 to <18 years of age, as assessed by differences in seroconversion rates for each of the four vaccine strains separately after vaccination. The study was to be considered a success if both co-primary immunogenicity objectives were achieved.

Selected Secondary Immunogenicity Objective

- To evaluate the antibody responses to all four influenza vaccine strains after vaccination according to the Center for Biologics Evaluation and Research (CBER) criteria.

Safety Objective

- To evaluate the safety and tolerability of QIVc, TIV1c, and TIV2c in subjects ≥4 years to <18 years of age.

6.2.2 Design Overview

This was a phase 3, randomized, double-blind, multicenter, noninferiority study to evaluate the immunogenicity and safety of QIVc, TIV1c, and TIV2c in subjects ≥4 years to <18 years of age. Both "previously vaccinated" and "not previously vaccinated" subjects were to be enrolled in this study. The definitions of "previously vaccinated" and "not previously vaccinated" subjects for the purposes of this study are as follows:

"Previously Vaccinated" Subjects:

- Any child 9 years of age and older
- Any child under the age of 9 years who has received 2 or more doses of seasonal influenza vaccine since July 1, 2010

"Not Previously Vaccinated" Subjects:

- Any child under the age of 9 years who does not meet the conditions for "previously vaccinated" (including fewer than 2 doses given since 2010 or receipt of exclusively nonseasonal [pandemic] influenza vaccines)
- Any child under the age of 9 years with unknown influenza vaccination history.

Subjects ≥4 to <9 years of age who were "not previously vaccinated" were to receive two vaccinations separated by approximately 4 weeks. Subjects ≥4 to <9 years of age who were "previously vaccinated" and subjects ≥9 to <18 years of age were to receive one vaccination. All subjects were to be evaluated for safety and immunogenicity. Approximately 2352 subjects ≥4 to <18 years of age (2000 evaluable subjects, assuming a dropout rate of 15%) were to be enrolled in a 1:1 stratified fashion into 2 age cohorts: ≥4 years to <9 years of age and ≥9 years to <18 years of age. Subjects between ≥4 to <9 years of age were to be further stratified by previous influenza vaccine status as

"previously vaccinated" and "not previously vaccinated." Within each treatment arm, at least 30% and not more than 50% of subjects who were "previously vaccinated" against influenza were to be enrolled. Subjects were to be randomized at an approximate 2:1:1 ratio to receive QIVc, TIV1c, or TIV2c vaccine.

The study was conducted between November 7, 2013 and August 13, 2014.

6.2.3 Population

Healthy subjects 4 through 17 years of age were enrolled in the study.

6.2.4 Study Treatments or Agents Mandated by the Protocol

The vaccine formulations and lots used in the study were the same as those in Study V130_01. Please refer to Section 6.1.4 for details.

6.2.6 Sites and Centers

The study was conducted in 90 centers in the United States.

6.2.7 Surveillance/Monitoring

Please refer to the clinical review.

6.2.8 Endpoints and Criteria for Study Success

Immunogenicity

Similar to Study V130_01, the primary immunogenicity endpoints used in the study were:

- GMT of all 4 influenza strains as measured on day 1, day 22 ("previously vaccinated" subjects) and day 50 ("not previously vaccinated" subjects).
- Ratio of GMT as calculated at day 22 ("previously vaccinated" subjects) and at day 50 ("not previously vaccinated" subjects):
    - A/H1N1: TIV1c/QIVc
    - A/H3N2: TIV1c/QIVc
    - B1: TIV1c/QIVc (noninferiority comparison), TIV2c/QIVc (superiority comparison)
    - B2: TIV2c/QIVc (noninferiority comparison), TIVc1/QIVc (superiority comparison)
- Percentages of subjects achieving seroconversion and HI titer ≥1:40 as calculated for all four influenza strains on day 1, day 22 ("previously vaccinated" subjects), and day 50 ("not previously vaccinated" subjects).
    - Differences in percentages of subjects achieving seroconversion as calculated at day 22 ("previously vaccinated" subjects) and at day 50 ("not previously vaccinated" subjects):
        - A/H1N1: TIV1c-QIVc
        - A/H3N2: TIV1c-QIVc
        - B1: TIV1c-QIVc
        - B2: TIV2c- QIVc

Success Criteria for Primary Objectives

Noninferiority objectives regarding GMTs (3 weeks after last vaccination)
The upper bound of the 2-sided 95% CI for the ratio of GMTs (GMT_{TIV1c} or $_{TIV2c}$/GMT_{QIVc}) for HI antibody should not exceed the noninferiority margin of 1.5.

Noninferiority objective regarding seroconversion (3 weeks after last vaccination)
The upper bound of the 2-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV1c or TIV2c – % seroconversion QIVc) for HI antibody should not exceed the margin of 10%.

The study was to be considered a success if both co-primary noninferiority immunogenicity objectives were achieved.

Safety
The safety endpoints were:

- Percentages of subjects with solicited local and systemic AEs and other solicited data as measured for 7 days following each vaccination and calculated for 4 time intervals after each vaccination: 30 minutes, day 1 through day 3 (with and without 30 min), day 4 through day 7 (with and without 30 min), day 1 through day 7 (with and without 30 min).
- Percentages of subjects with unsolicited AEs were assessed from day 1 through 3 weeks after last vaccination (day 22 in "previously vaccinated" subjects, day 50 in "not previously vaccinated" subjects).
- Percentage of subjects reporting SAEs, medically attended AEs, AEs leading to withdrawal from the study, NOCDs, and concomitant medications associated with these events as collected from day 1 through 6 months after last vaccination (day 181 for "previously vaccinated" subjects and day 210 for "not previously vaccinated" subjects).

6.2.9 Statistical Considerations & Statistical Analysis Plan

Analysis Populations
The following analysis populations were considered:

- *Full Analysis Set Immunogenicity Set* (FAS) included all subjects who received at least one study vaccination. The FAS immunogenicity set included these subjects who provided immunogenicity data at day 1 and day 22 (day 50 for not previously vaccinated subjects). FAS populations were to be analyzed "as randomized."
- The Per Protocol Set (PPS) included all subjects in the FAS set who correctly received the vaccine and had no major protocol deviations, such as withdrawal, informed consent, or experiencing ILI- and RT-PCR-confirmed influenza during the treatment period.
- The Safety Set included all subjects who provided relevant safety data. The safety set population was analyzed "as treated."

Analysis of Primary Objectives
The primary noninferiority testing was conducted in subjects ages ≥4 to <18 years using the 3 weeks after last vaccination HI titer, which corresponds to day 22 for "previously vaccinated" and day 50 for "not previously vaccinated" subjects, and the PPS.

For GMT comparison, Log10 transformed individual HI titers as measured at 3 weeks after last vaccination (day 22 and day 50) were modeled using an analysis of covariance (ANCOVA) model, with factors for age cohort (≥4 to <9 years of age and ≥9 to <18 years of age), vaccine group, center, and a covariate for the log-transformed prevaccination antibody titer (baseline). Geometric means, GMT ratios, and corresponding two-sided 95% CIs were calculated based on this model.

For seroconversion rate comparison, the vaccine group difference (seroconversion comparator TIVc – seroconversion QIVc) in the percentage of subjects achieving seroconversion was calculated using a binomial distribution. The two-sided 95% CIs were constructed using the Miettinen and Nurminen method.

In addition, as a secondary analysis, the numbers and percentages of subjects achieving seroconversion and percentages of subjects achieving an HI titer ≥1:40, with point estimates and two-sided 95% CIs, were computed using the Clopper-Pearson method for each strain. The lower bounds of the 95% CIs were to be compared to the corresponding threshold according to the CBER criteria.

Analysis of Safety Objectives
Safety endpoints were analyzed in a descriptive manner.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

A total of 2333 subjects were enrolled into the study. Of these, 1159 subjects were enrolled in the QIVc group, 593 subjects in TIV1c group, and 581 subjects in the TIV2c group.

6.2.10.1.1 Demographics

Demographic and other baseline characteristics were well balanced among the QIVc, TIV1c, and TIV2c groups (Table 13). Across all groups, the mean age of subjects was ~9.5 years; weight ~40 to 41 kg; and height ~139 cm. The majority of the enrolled subjects in the 3 groups were Caucasian (53% to 54%), followed by Black (20% to 23%), and Hispanic (19% to 21%). The percentages of male and female subjects were similar across the three groups.

Table 13: Demographic Characteristics in Study V130_03

	QIVc (N=1159)	TIV1c (N=593)	TIV2c (N=581)
Age (years)±SD	9.5±3.8	9.5±3.8	9.3±3.7
≥4-<9 years	575 (49.6%)	293 (49.4%)	294 (50.6%)
9 years and older	584 (50.4%)	300 (50.6%)	287 (49.4%)
Sex			
Male	603 (52%)	309 (52%)	297 (51%)
Female	556 (48%)	284 (48%)	284 (49%)
Height (cm) ±SD	139.4±22.14	139.3±21.26	139.0±21.39
Weight (kg) ±SD	40.8±21.95	40.6±20.69	40.4±20.97
Body Mass Index (kg/m^2)±SD	19.6±5.34	19.6±5.26	19.6±5.76
Race/Ethnicity			
Asian	7 (<1%)	2 (<1%)	2 (<1%)
American Indian	4 (<1%)	4 (<1%)	6 (1%)
Black	261 (23%)	131 (22%)	118 (20%)
Caucasian	614 (53%)	321 (54%)	308 (53%)
Hispanic	227 (20%)	114 (19%)	122 (21%)
Native Hawaiian	5 (<1%)	1 (<1%)	5 (<1%)
Other	41 (4%)	20 (3%)	20 (3%)
Previous influenza Vaccination	819 (71%)	420 (71%)	400 (69%)

Source: Tables 11.2-1 and 14.1.1.1.1.4; Clinical Study Report V130_03.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Healthy subjects were enrolled in the study.

6.2.10.1.3 Subject Disposition
A summary of the subject disposition is provided in Table 14. The FAS included 2236 (96% of the enrolled population). Of these, 210 subjects were excluded from the PPS. PPS was composed of 2026 (87% of the enrolled population). Among all groups, the most common major protocol deviation was noncompliance with blood draw schedules in 132 (6%) subjects. Other common major protocol deviations were unavailability of serological results in 74 (3%) subjects, noncompliance with study vaccination schedule in 62 (3%) subjects, missing second vaccination in 35 (2%) subjects, no blood draw at day 50 in 17 (<1%) subjects, and no blood draw at day 22 in 6 (<1%) subjects.

Table 14: Disposition of Study Subjects in Study V130_03

Vaccine Group	QIVc	TIV1c	TIV2c
Enrolled (N)	1159	593	581
Exposed	1159 (100%)	593 (100%)	580 (100%)
Completed	1091 (94%)	560 (94%)	545 (94%)
Premature Withdrawals	68 (6%)	33 (6%)	36 (6%)
Adverse Event	0	1 (<1%)	0
Withdrawal by subject	13 (1%)	7 (1%)	8 (1%)
Lost to follow-up	46 (4%)	22 (4%)	26 (4%)
Administrative reasons	2 (<1%)	0	0
Other	7 (<1%)	3 (<1%)	2 (<1%)
Safety Set	1149	579	570
Subjects with at least one major protocol deviation	140 (12%)	80 (13%)	75 (13%)
Full Analysis Set (FAS)	1113 (96%)	566 (95%)	557 (96%)
Per Protocol Set (PPS)	1014 (87%)	510 (86%)	502 (86%)

Source: Tables 10.1-1, 10.2-1 and 11.1-1; Clinical Study Report V130_03.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The analysis results for the primary endpoints are presented in Table 15 for the post-vaccination GMT comparisons and in Table 16 for the comparisons of seroconversion rates. The results were compared between the QIVc and TIV1c groups for the H1N1, H3N2, and B1 strains, whereas they were compared between the QIVc and TIV2c groups for the B2 strain. For all four strains, the upper bounds of the two-sided 95% CIs for the ratios of GMTs ($GMT_{TIV1c \text{ or } TIV2c}$ /GMT_{QIVc}) for HI antibody at day 22 or day 50 remained within the noninferiority margin of 1.5 (1.14 for A/H1N1, 1.14 for A/H3N2, 1.1 for B1, and 1.14 for B2 influenza strains). For all four influenza strains, the upper bounds of the 2-sided 95% CIs on the differences between the seroconversion rates (%seroconversion TIV1c or TIV2c – % seroconversion QIVc) for HI antibody also remained within the noninferiority margin of 10% (6.9% for A/H1N1, 9.2% for A/H3N2, 4.5% for B1, and 3.2% for B2 influenza strains). Therefore, the primary objectives were met.

Table 15: Primary Analysis of Ratios of HI Geometric Mean Titers 3 Weeks after Vaccination - Per Protocol Set

Strain	QIVc GMT (95% CI)	TIV1c /TIV2c* GMT	GMT Ratio (95% CI)
H1N1	N=1014 1090 (1027-1157)	N=510 1125 (1034-1224)	1.03 (0.93-**1.14**)
H3N2	N=1013 738 (703-774)	N=510 776 (725-831)	1.05 (0.97-**1.14**)
B1	N=1013 155 (146-165)	N=510 154 (141-168)	0.99 (0.89-**1.1**)
B2	N=1009 185 (171-200)	N=501 185 (166-207)	1.00 (0.87-**1.14**)

*For H1N1, H3N2, and B1 strains, ratios of GMTs were calculated as TIV1c/QIVc. For the B2 strain, ratio of GMTs was calculated as TIV2c/QIVc.
Source: Adapted from Table 11.4.1-1; Clinical Study Report V130_03.

Table 16: Primary Analysis of Seroconversion Rates at 3 Weeks after Vaccination - Per Protocol Set

Strain	QIVc n (%) (95% CI)	TIV1c or TIV2c * n (%) (95% CI)	Difference (95% CI)
H1N1	N=1014 732 (72%) (69%, 75%)	N=510 380 (75%) (70%-78%)	2% (-2.5%- 6.9%)
H3N2	N=1013 473 (47%) (44%, 50%)	N=510 258 (51%) (46%-55%)	4% (-1.4%- 9.2%)
B1	N=1013 672 (66%) (63%, 69%)	N=510 336 (66%) (62%-70%)	0% (-5.5%- 4.5%)
B2	N=1009 735 (73%) (70%, 76%)	N=501 357 (71%) (67%-75%)	-2% (-6.5%- 3.2%)

*For H1N1, H3N2, and B1 strains, differences in seroconversion rate were calculated as TIV1c - QIVc. For the B2 strain, difference in seroconversion rate was calculated as TIV2c - QIVc.
Source: Adapted from Table 11.4.1-2; Clinical Study Report V130_03.

6.2.11.2 Analyses of Secondary Endpoints

Table 17 presents the results for the analysis of the immunogenicity endpoints against the CBER criteria for both the PPS and FAS populations. Both CBER immunogenicity criteria for seroconversion and HI titer ≥1:40 were met for all four influenza strains.

Table 17: Analysis of Post-vaccination Results in the QIVc Group According to CBER Criteria

	PPS	FAS	PPS	FAS
Parameter	**# (%) of subjects seroconverted (95% CI)**	**# (%) of subjects seroconverted (95% CI)**	**# (%) of subjects with HI titer ≥1:40 (95% CI)**	**# (%) of subjects with HI titer ≥1:40 (95% CI)**
H1N1	N=1014 732 (72%) (69%, 75%)	N=1113 812 (73%) (70%, 76%)	N=1014 1005 (99%) (98%, 100%)	N=1113 1104 (99%) (98%, 100%)
H3N2	N=1013 473 (47%) (44%, 50%)	N=1112 527 (47%) (44%, 50%)	N=1013 1010 (100%) (99%, 100%)	N=1112 1109 (100%) (99%, 100%)
B1	N=1013 672 (66%) (63%, 69%)	N=1112 743 (67%) (64%, 70%)	N=1013 942 (93%) (91%, 94%)	N=1112 1028 (92%) (91%, 94%)
B2	N=1009 735 (73%) (70%, 76%)	N=1108 809 (73%) (70%, 76%)	N=1009 925 (92%) (90%, 93%)	N=1108 1009 (91%) (89%, 93%)

Source: Adapted from Tables 11.4.1-2, 14.2.1.1.1; Clinical Study Report V130_03.

6.2.11.3 Subpopulation Analyses

Please see section 7.

6.2.11.4 Dropouts and/or Discontinuations

The dropout rate in the study was low. It is unlikely that the missing data would have a notable, qualitative effect on the study conclusions.

6.2.11.5 Exploratory and Post Hoc Analyses

N/A

6.2.12 Safety Analyses

Of the 2333 subjects enrolled into the study, 2332 subjects were exposed to study vaccination and were included in the safety set. The safety set for solicited AEs from 30 minutes through day 7 included 97% of the enrolled population

Solicited Adverse Events

The percentages of subjects in the QIVc, TIV1c, and TIV2c groups who reported solicited local AEs were 66%, 65%, and 60%, and solicited systemic AEs were 38%, 39%, and 34%, respectively.

Table 18: Number (%) of Subjects ≥4 to <18 Years of Age with Solicited Adverse Events from Day 1 through Day 7 Any Last Vaccination- Solicited Safety Set

Vaccine Group	QIVc (N=1135)	TIV1c (N=570)	TIV2c (N=563)
Any	819 (72%)	406 (71%)	375 (67%)
Local	749 (66%)	370 (65%)	338 (60%)
Systemic	436 (38%)	222 (39%)	191 (34%)
Others	101 (9%)	52 (9%)	46 (8%)

Source: Table 12.2.1-1; Clinical Study Report V130_03.

Unsolicited Adverse Events

In the overall population ≥4 to <18 years of age, percentages of subjects who reported unsolicited AEs in the QIVc, TIV1c, and TIV2c groups within 22 days after the last vaccination were comparable (24.3%, 24.0%, and 26.7%, respectively). The percentages of AEs judged by the investigator as possibly related to the study vaccine across the QIVc, TIV1c, and TIV2c groups were also comparable (4.9%, 5.9%, and 5.4%, respectively). A total of 15 subjects (6 [0.5%] from the QIVc group, 7 [1.2%] from the TIV1c group, and 2 [0.4%] from the TIV2c group) reported 20 SAEs during the entire course of the study. No SAE was judged by the investigator to be related to the study vaccines.

Table 19: Number (%) of Subjects with Unsolicited Adverse Events - Unsolicited Safety Set

Vaccine Group	QIVc N=1149	TIV1c N=579	TIV2c N=570
Any AE	279 (24.3%)	139 (24.0%)	152 (26.7%)
At least Possibly related AE	56 (4.9%)	34 (5.9%)	31 (5.4%)
SAE	6 (0.5%)	7 (1.2%)	2 (0.4%)
At least possibly related SAE	0	0	0
AE leading to study withdrawal	0	1 (0.2%)	0
Medically attended AE	310 (27.0%)	156 (26.9%)	153 (26.8)
NOCD	20 (1.7%)	11 (1.9%)	11 (1.9%)
Death	0	0	0

Source: Table 12.2.1-4; Clinical Study Report V130_03

6.2.12.1 Methods

Please refer to the clinical review.

6.2.12.3 Deaths

There were no deaths reported in the study.

6.2.12.4 Nonfatal Serious Adverse Events

Overall, 15 subjects experienced a total of 20 SAEs (6 [0.5%] subjects in the QIVc, 7 [1.2%] in the TIV1c, and 2 [0.4%] in the TIV2c groups). All the SAEs were judged by the investigator to be unrelated to the study vaccine.

6.2.12.5 Adverse Events of Special Interest (AESI)

Please refer to the clinical review.

6.2.12.6 Clinical Test Results

N/A

6.2.12.7 Dropouts and/or Discontinuations

One subject, # 1401046, from the TIV1c group withdrew from the study at day 10 due to an AE (prolonged erythema and induration at injection-site). In the opinion of the investigator, the event was probably related to the study vaccine.

6.2.12.8 Safety Subgroup Analyses

Table 20 presents a summary of unsolicited AEs by sex. The AE rates were similar in the two sex groups.

Table 21 presents a summary of unsolicited AEs by race/ethnicity origin. Similar to the finding observed in the adults (see Section 6.1.12.8), the overall AE rate appeared to be slightly higher among Caucasians than among Blacks and Hispanics. The rates in the other categories were similar across the racial groups.

Table 20: Unsolicited Adverse Events in Subjects 4 through 17 Years of Age by Sex – Unsolicited Safety Set

	Female	**Female**	**Female**	**Male**	**Male**	**Male**
n (%)	**QIVc (N = 551)**	**TIV1c (N = 276)**	**TIV2c (N=274)**	**QIVc (N = 598)**	**TIV1c (N = 303)**	**TIV2c (N=296)**
Any AE	242 (43.9)	120 (43.5)	134 (48.9)	252 (42.1)	131 (43.2)	115 (38.9)
Possibly/probably related AE	31 (5.6)	21 (7.6)	19 (6.9)	28 (4.7)	16 (5.3)	13 (4.4)
Any SAE	5 (0.9)	2 (0.7)	0	1 (0.2)	5 (1.7)	2 (0.7)
Possibly/probably related SAE	0	0	0	0	0	0
AEs leading to premature withdrawal	0	1 (0.4)	0	0	0	0
Medically attended AE	154 (27.9)	64 (23.2)	77 (28.1)	156 (26.1)	92 (30.4)	76 (25.7)
NOCD	10 (1.8)	3 (1.1)	2 (0.7)	10 (1.7)	8 (2.6)	9 (3.0)
Deaths	0	0	0	0	0	0

Source: CSR V130_03: Table 14.3.1.15.4; Table 14.3.1.19.4; Table 14.3.2.2.4; Table 14.3.2.3.4; Table 14.3.2.4.4; Table 14.3.2.8, Table 14.3.2.6.4, Table 14.3.2.7.4.

Table 21: Unsolicited Adverse Events in Subjects 4 through 17 Years of Age by Race/Ethnicity – Unsolicited Safety Set

	Black	Black	Black	Caucasian	Caucasian	Caucasian	Hispanic	Hispanic	Hispanic
n (%)	**QIVc (N =175)**	**TIV1c (N = 77)**	**TIV2c (N=80)**	**QIVc (N = 1005)**	**TIV1c (N =519)**	**TIV2c (N=523)**	**QIVc (N = 120)**	**TIV1c (N =59)**	**TIV2c (N=52)**
Any AE	71 (27.6)	45 (35.4)	28 (24.3)	293 (48.0)	155 (48.6)	159 (52.6)	101 (45.1)	41 (38.7)	46 (38.3)
Possibly/probably related AE	15 (5.8)	5 (3.9)	2 (1.7)	27 (4.4)	21 (6.6)	18 (6.0)	14 (6.3)	9 (8.5)	8 (6.7)
Any SAE	1 (0.4)	1 (0.8)	0	3 (0.5)	6 (1.9)	2 (0.7)	1 (0.4)	0	0
Possibly/probably related SAE	0	0	0	0	0	0	0	0	0
AEs leading to premature withdrawal	0	0	0	0	1 (0.3)	0	0	0	0
Medically attended AE	32 (12.5)	21 (16.5)	15 (13.0)	189 (30.9)	94 (29.5)	95 (31 5)	69 (30.8)	32 (30.2)	32 (26.7)
NOCD	0	1 (0.8)	2 (1.7)	10 (1.6)	8 (2.5)	7 (2.3)	6 (2.7)	1 (0.9)	2 (1.7)
Deaths	0	0	0	0	0	0	0	0	0

Source: CSR V130_01: Table 14.3.1.13.7, Table 14.3.1.18.7, Table 14.3.2.3.6, Table 14.3.2.11, Table 14.3.2.5.7, Table 14.3.2.6.7, Listing 16.2.4.1.

7. INTEGRATED OVERVIEW OF EFFICACY

The subgroup analyses of the immunogenicity results from studies V130_01 and V130_03 by age, sex, and race are summarized in this section. The primary endpoints – GMT and seroconversion rate-- and their corresponding 95% CIs in each subgroup are presented. It should be noted that the studies were likely not powered for making comparisons within subgroups. The results presented here are for descriptive purpose only.

By Age

Table 22 and 23 present the subgroup immunogenicity analysis by age group in the per-protocol sets of the two studies. The immune responses were similar in the QIVc group and the corresponding TIVc group. As age increased, the immune responses tended to decrease.

Table 22: Immunogenicity Results at 3 Weeks after Vaccination in Subjects 18 Years of Age and Older, by Age, HI Assay – PPS

		18-64 years	18-64 years	≥65 years	≥65 years
Strain	**Day 22**	**QIVc (N=629)**	**TIVc1/TIVc2 (N=309/316)**	**QIVc (N=1250)**	**TIVc1/TIVc2 (N=635/639)**
H1N1	GMT (95% CI)	472.2 (429.4, 519.2)	432.2 (374.7, 498.5)	193.1 (175.3, 212.8)	210.7 (184.8, 240.2)
H1N1	Seroconversion Rate (95% CI)	63.3% (59.4, 67.1)	60.2% (54.5, 65.7)	34.9% (31.2, 38.8)	37.7% (32.4, 43.2)
H3N2	GMT (95% CI)	414.1 (379.4, 452.0)	410.5 (361.5, 466.0)	334.2 (304.5, 366.9)	350.3 (306.7, 400.0)
H3N2	Seroconversion Rate (95% CI)	49.1% (45.2, 53.1)	46.6% (40.9, 52.3)	27.4% (20.5, 30.2)	25.2% (20.5, 30.2)
B1	GMT (95% CI)	186.6 (171.0, 203.5)	167.7 (149.5, 188.1)	94.7 (87.5, 102.4)	81.3 (73.1, 90.4)
B1	Seroconversion Rate (95% CI)	52.0% (48.0, 56.0)	50.5% (44.8, 56.2)	20.9% (17.8, 24.3)	19.9% (15.7, 24.7)
B2	GMT (95% CI)	225.9 (208.9, 244.3)	198.4 (176.9, 222.5)	138.6 (128.5, 149.5)	136.2 (122.2, 151.9)
B2	Seroconversion Rate (95% CI)	52.5% (48.5, 56.4)	50.3% (44.7, 56.0)	26.9% (23.4, 30.6)	20.7% (16.5, 25.6)

Source: CSR V130_01 Table 14.2.1.2.4 and Table 14.2.1.3.4.

Table 23: Immunogenicity Results at 3 Weeks after Vaccination in Subjects 4 through 17 Years of Age, by Age, HI Assay – PPS

		4-8 years	4-8 years	9-17 years	9-17 years
Strain	**Day 22/Day 50***	**QIVc (N=467)**	**TIVc1/TIVc2 (N=238)**	**QIVc (N=546~547)**	**TIVc1/TIVc2 (N=272)**
H1N1	GMT (95% CI)	1042 (962-1130)	1109 (990-1242)	1139 (1045-1242)	1138 (1007-1286)
H1N1	Seroconversion Rate (95% CI)	75% (71%-79%)	77% (71%-82%)	70% (66%-74%)	72% (67%-78%)
H3N2	GMT (95% CI)	758 (707-813)	782 (709-863)	719 (673-767)	762 (694-836)
H3N2	Seroconversion Rate (95% CI)	52% (47%-56%)	48% (42%-55%)	42% (38%-47%)	53% (46%-59%)
B1	GMT (95% CI)	117 (106-128)	116 (102-132)	200 (185-218)	200 (178-224)
B1	Seroconversion Rate (95% CI)	71% (66%-75%)	69% (63%-75%)	63% (58%-67%)	63% (57%-69%)
B2	GMT (95% CI)	161 (143-181)	166 (141-195)	212 (192-235)	203 (175-234)
B2	Seroconversion Rate (95% CI)	74% (70%-78%)	75% (69%-80%)	72% (68%-75%)	68% (62%-74%)

**Day 22 for previously vaccinated subjects, Day 50 for not previously vaccinated subjects.*
Source: CSR V130_03, Table 14.2.1.1.5, Table 14.2.1.1.5.1, Table 14.2.1.2.5, Table 14.2.1.2.5.1, Table 14.2.1.3.5 and Table 14.2.1.3.5.1.

By Sex

Table 25 presents subgroup immunogenicity analysis by sex within the age groups in the per-protocol sets of the two studies. The immune responses were similar in the QIVc group and the corresponding TIVc group, within females and within males. The immune responses appear to be also comparable in males and females.

Table 24: Immunogenicity Results at 3 Weeks after Vaccination in Subjects 18 Years of Age and Older, by Sex, HI Assay – PPS

		Females	Females	Males	Males
Strain	**Day 22**	**QIVc (N=689)**	**TIVc1/TIVc2 (N=370/381)**	**QIVc (N=561)**	**TIVc1/TIVc2 (N=265/258)**
H1N1	GMT (95% CI)	306.5 (278.5-337.3)	286.0 (250.1-326.9)	298.4 (267.4-333.1)	317.9 (273.0-370.2)
H1N1	Seroconversion Rate (95% CI)	50.1% (46.3%-53.9%)	48.4% (43.2%-53.6%)	48.1% (43.9%-52.4%)	49.1% (42.9%-55.2%)
H3N2	GMT (95% CI)	390.5 (359.5-424.2)	382.7 (341.8-428.5)	351.1 (317.5-388.1)	372.4 (319.1-434.6)
H3N2	Seroconversion Rate (95% CI)	37.9% (34.2%-41.6%)	33.2% (28.5%-38.3%)	38.9% (34.8%-43.0%)	38.9% (33.0%-45.0%)
B1	GMT (95% CI)	125.8 (115.8-136.7)	111.6 (99.9-124.5)	142.9 (130.4-156.6)	121.6 (107.1-137.9)
B1	Seroconversion Rate (95% CI)	36.3% (32.7%-40.0%)	31.9% (27.2%-36.9%)	36.9% (32.9%-41.0%)	38.9% (33.0%-45.0%)
B2	GMT (95% CI)	162.0 (150.4-174.6)	161.9 (146.2-179.3)	197.9 (181.9-215.3)	167.2 (146.9-190.4)
B2	Seroconversion Rate (95% CI)	38.9% (35.2%-42.7%)	34.9% (30.1%-39.9%)	40.8% (36.7%-45.0%)	36.0% (30.2%-42.2%)

Source: CSR V130_01 Table 14.2.1.1.1, Table 14.2.1.2.1 and Table 14.2.1.3.1

Table 25: Immunogenicity Results at 3 Weeks after Vaccination in Subjects 4 through 17Years of Age and above, by Sex, HI Assay – PPS

		Females	Females	Males	Males
Strain	**Day 22/Day 50**	**QIVc (N=478~480)**	**TIVc1/TIVc2 (N=243/241)**	**QIVc (N=531~534)**	**TIVc1/TIVc2 (N=267/260)**
H1N1	GMT (95% CI)	1138 (1045-1239)	1173 (1041-1322)	1052 (967-1144)	1089 (967-1226)
H1N1	Seroconversion Rate (95% CI)	72% (67%-76%)	72% (65%-77%)	73% (69%-76%)	77% (72%-82%)
H3N2	GMT (95% CI)	736 (686-789)	834 (756-921)	735 (688-785)	723 (659-794)
H3N2	Seroconversion Rate (95% CI)	47% (43%-52%)	49% (43%-55%)	46% (42%-50%)	52% (46%-58%)
B1	GMT (95% CI)	171 (157-187)	174 (154-197)	144 (132-157)	140 (124-158)
B1	Seroconversion Rate (95% CI)	66% (62%-70%)	61% (55%-67%)	66% (62%-70%)	70% (64%-75%)
B2	GMT (95% CI)	186 (166-208)	189 (161-222)	187 (168-207)	182 (157-212)
B2	Seroconversion Rate (95% CI)	71% (67%-75%)	70% (63%-75%)	74% (70%-78%)	73% (67%-78%)

**Day 22 for previously vaccinated subjects, Day 50 for not previously vaccinated subjects*
Source: CSR V130_03, Table 14.2.1.1.2, Table 14.2.1.1.2.1, Table 14.2.1.2.2, Table 14.2.1.2.2.1, Table 14.2.1.3.2 and Table 14.2.1.3.2.1.

By Race

Table 26 and Table 27 present subgroup immunogenicity analysis by sex within the age groups in the per-protocol sets of the two studies. The immune responses were similar in the QIVc group and the corresponding TIVc group within each racial group. It appears that the immune responses among Caucasians tended to be lower than those in Blacks and Hispanics.

Table 26: Immunogenicity Results at 3 Weeks after Vaccination in Subjects 18 Years of Age and Older, by Race, HI Assay – PPS

		Black	Black	Caucasian	Caucasian	Hispanic	Hispanic
Strain	**Day 22**	**QIVc (N=163)**	**TIVc1/TIVc2 (N=73/N=73)**	**QIVc (N=951)**	**TIVc1/TIVc2 (N=491/506)**	**QIVc (N=113)**	**TIVc1/TIVc2 (N=54/50)**
H1N1	GMT (95% CI)	514.2 (425.7-621.0)	463.4 (330.9-649.0)	267.8 (246.5-290.9)	262.8 (235.0-293.8)	365.1 (295.1-451.7)	432.7 (323.4-578.9)
H1N1	Seroconversion Rate (95% CI)	63.8% (55.9%-71.2%)	63.0% (50.9%-74.0%)	44.9% (41.7%-48.1%)	45.0% (40.5%-49.5%)	63.7% (54.1%-72.6%)	53.7% (39.6%-67.4%)
H3N2	GMT (95% CI)	469.2 (392.8-560.4)	474.6 (367.1-613.6)	350.0 (325.9-377.0)	355.2 (320.2-394.2)	426.9 (341.7-533.5)	511.2 (365.7-714.6)
H3N2	Seroconversion Rate (95% CI)	52.1% (44.2%-60.0%)	52.1% (40.0%-63.9%)	35.0% (32.0%-38.1%)	32.4% (28.3%-36.7%)	48.7% (39.2%-58.3%)	38.9% (25.9%-53.1%)
B1	GMT (95% CI)	243.8 (206.0-288.5)	215.8 (171.3-271.8)	115.3 (107.8-123.4)	101.9 (92.9-111.7)	161.5 (132.3-197.1)	139.8 (103.5-188.9)
B1	Seroconversion Rate (95% CI)	60.1% (52.2%-67.7%)	56.2% (44.1%-67.8%)	29.9% (27.0%-32.9%)	30.3% (26.3%-34.6%)	56.6% (47.0%-65.9%)	40.7% (27.6%-55.0%)
B2	GMT (95% CI)	268.2 (231.4-310.9)	222.0 (172.4-286.0)	161.1 (151.1-171.7)	153.2 (140.1-167.6)	208.3 (174.3-248.9)	215.6 (166.2-279.6)
B2	Seroconversion Rate (95% CI)	59.5% (51.6%-67.1%)	50.7% (38.7%-62.6%)	34.7% (31.7%-37.8%)	29.8% (25.9%-34.0%)	51.3% (41.7%-60.8%)	68.0% (53.3%-80.5%)

Source: CSR V130_01 Table 14.2.1.1.2, Table 14.2.1.2.2 and Table 14.2.1.3.2

Table 27: Immunogenicity Results at 3 Weeks after Vaccination in Subjects 4 through 17 Years of Age, by Race, HI Assay – PPS

		Black	Black	Caucasian	Caucasian	Hispanic	Hispanic
Strain	**Day 22/50***	**QIVc (N=221~222)**	**TIVc1/TIVc2 (N=102~105)**	**QIVc (N=545~548)**	**TIVc1/TIVc2 (N=265~284)**	**QIVc (N=194)**	**TIVc1/TIVc2 (N=94~106)**
H1N1	GMT (95% CI)	1158 (1042-1288)	1314 (1126-1533)	1046 (959-1141)	1035 (918-1167)	1183 (1035-1351)	1244 (1028-1507)
H1N1	Seroconversion Rate (95% CI)	68% (61%-74%)	70% (60%-78%)	75% (71%-79%)	79% (73%-83%)	73% (66%-79%)	68% (58%-77%)
H3N2	GMT (95% CI)	886 (809-970)	937 (821-1070)	689 (643-738)	739 (672-814)	709 (636-790)	697 (596-815)
H3N2	Seroconversion Rate (95% CI)	48% (41%-55%)	43% (33%-53%)	48% (44%-52%)	56% (50%-62%)	42% (35%-50%)	44% (33%-54%)
B1	GMT (95% CI)	206 (184-231)	192 (163-226)	150 (137-164)	143 (126-162)	136 (118-156)	155 (126-190)
B1	Seroconversion Rate (95% CI)	73% (67%-79%)	66% (56%-75%)	64% (60%-68%)	66% (60%-72%)	66% (59%-73%)	66% (55%-75%)
B2	GMT (95% CI)	217 (188-251)	229 (185-284)	186 (166-207)	172 (147-201)	171 (143-204)	195 (153-248)
B2	Seroconversion Rate (95% CI)	75% (68%-80%)	73% (63%-81%)	73% (69%-77%)	71% (65%-77%)	72% (65%-78%)	71% (61%-79%)

** Day 22 for previously vaccinated subjects, Day 50 for not previously vaccinated subjects.*
Source: CSR V130_03, Table 14.2.1.1.3, Table 14.2.1.1.3.1, Table 14.2.1.2.3, Table 14.2.1.2.3.1, Table 14.2.1.3.3 and Table 14.2.1.3.3.1

8. INTEGRATED OVERVIEW OF SAFETY

N/A

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Included in this supplemental application were clinical data from studies V130_01 and V130_03. The goals were to demonstrate in the target populations a similar safety profile and noninferior immunogenicity of the vaccine compared to Flucelvax® vaccine, and to establish that the presence of a second B strain did not interfere with immune responses elicited by the other B strain or the two A strains. Study V130_01 was conducted among subjects 18 years of age and older, while Study V130_03 was conducted among subjects 4 through 17 years of age. In both studies, the primary immunogenicity objectives of noninferiority were met. There were no apparent safety concerns.

10.2 Conclusions and Recommendations

The submitted data support noninferiority in immunogenicity of QIVc compared to the relevant TIVc for both age groups 4 through 17 years and 18 years and older. However, for age group 4 through 17, the inferred effectiveness of QIVc depends on the approval of TIVc in this age group. Without the approval of TIVc in subjects 4 through 17 years of age, the conclusion regarding the inferred effectiveness of QIVc through demonstration of immunogenic noninferiority to TIVc cannot be drawn.