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Application Type	Efficacy Supplement
STN	125408.127
CBER Received Date	21-April-2015
PDUFA Goal Date	23-May-2016
Division / Office	DVRPA/OVRR
Priority Review	No
Reviewer Name(s)	Ralph LeBlanc, M.D., Ph.D. Medical Officer Clinical Review Branch 1
Review Completion Date / Stamped Date	20 May-2016
Supervisory Concurrence	Jeff Roberts, M.D. Chief, Clinical Review Branch 1
	Lucia Lee, M.D., Team Leader, Clinical Review Branch 1
Applicant	Seqirus, Inc.
Established Name	Influenza vaccine
(Proposed) Trade Name	Flucelvax Quadrivalent
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Each 0.5mL dose contains a total of 60 micrograms (mcg) hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 mcg HA of each of the four influenza strains contained in the vaccine.
Dosage Form(s) and Route(s) of Administration	0.5 mL single-dose pre-filled syringe; intramuscular injection
Dosing Regimen	4 through 8 years of age: one or two doses, depending upon prior influenza immunization; 9 years of age and older: one dose
Indication(s) and Intended Population(s)	Active immunization for the prevention of influenza disease caused by influenza A subtypes and type B viruses contained in the vaccine
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
BLA	biologics license application
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CSR	complete study report
DIS	Division of Inspections and Surveillance
eCTD	electronic Common Technical Document
ES	Executive Summary
FDAAA	Food and Drug Administration Amendments Act of 2007
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
OBE	Office of Biostatistics and Epidemiology
OCOD	Office of Communication Outreach and Development
OSE	Office of Surveillance and Epidemiology
PeRC	Pediatric Review Committee (CDER)
PI	package insert
PMC	post marketing commitment
PMR	post marketing requirement
PREA	Pediatric Research Equity Act
PVP	pharmacovigilance plan
RMS/BLA	regulatory management system for the biologics license application
SAE	serious adverse event

I. Executive Summary

Flucelvax Quadrivalent [QIV] is an inactivated seasonal influenza vaccine containing antigens from two influenza A subtype viruses (H1N1 and H3N2) and two influenza type B viruses. The safety and immunogenicity data contained in this supplemental biologics license application [sBLA] support an indication for active immunization against influenza disease caused by the Influenza A subtypes and type B viruses contained in the vaccine. The applicant's initial request for use of Flucelvax QIV in individuals 4 years of age and older was based on the demonstration of noninferior immunogenicity and comparable safety, in all age groups, to Flucelvax® (trivalent) vaccine ("traditional" approval regulatory pathway). Because the clinical data in the sBLA supported "traditional" approval only for the population 18 years of age and older, the applicant revised their request for use in individuals 4 to <18 years of age to be approved if the criteria for accelerated approval (21 CFR 601.41) were met.

Approval of Flucelvax QIV is based on safety and immunogenicity data from two clinical studies:

- V130_01: a randomized, controlled, double-blinded study in adults 18 years of age and older. Subjects received Flucelvax QIV or one of two formulations of the comparator trivalent influenza vaccine, Flucelvax (TIV1c or TIV2c)).

- V130_03: a randomized, controlled, double-blinded study in children 4 years to <18 years of age. Subjects received Flucelvax QIV or one of the two formulations of comparator trivalent influenza vaccine (TIV1c or TIV2c). Children 9 to <18 years of age received a single dose of Flucelvax QIV or comparator vaccine. Children 4 to <9 years of age received one or two doses (separated by 4 weeks) of Flucelvax QIV or comparator vaccine, based on determination of the subject's prior influenza vaccination history.

Flucelvax Trivalent (TIV) was the comparator vaccine used in both studies, and is licensed for the same indication and age groups, based on the same regulatory pathways described above for Flucelvax QIV (i.e., "traditional" approval for $\geq$18 years of age and accelerated approval 4 to <18 years of age). Since the clinical benefit of Flucelvax TIV in children 4 to <18 years of age has not been demonstrated in a confirmatory study, effectiveness of Flucelvax QIV cannot be inferred from immunogenicity bridging to Flucelvax TIV. However, the Flucelvax QIV data from children 4 to <18 years of age did support accelerated approval based on the criteria (herein referred to as "CBER criteria") described in the 2007 FDA Guidance for Industry "Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines".

Summary of Clinical Findings:
Immunogenicity

Study V130_01: The non inferiority criteria for the co-primary endpoints were met for all four influenza vaccine strains:
(a) The upper bound of the 2-sided 95% confidence interval (CI) for the ratios of GMTs (TIV1c or TIV2c/QIVc) for HI antibody were <1.5.

(b) The upper bound of the 2-sided 95% CI for the difference in seroconversion rates (TIV1c or TIV2c –QIVc) for HI antibody were <10%. Seroconversion was defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer ≥1:40 or a pre-vaccination HI titer >1:10 and at least 4-fold increase in serum HI antibody titer.

Study V130_03: Data from the secondary objective to demonstrate that QIVc met seroconversion criteria and percentage of subjects achieving HI titers ≥1:40 per CBER criteria for all four influenza vaccine strains. These data were adequate to support accelerated approval of Flucelvax QIV in children 4 to <18 years of age.

Safety
For both studies, the safety endpoints were solicited local and systemic adverse events from day 1 to day 7 post-vaccination; SAEs through 6 months after the last vaccination; and unsolicited AEs from day 1 to day 23 post-vaccination. In general, there were modestly higher frequencies of solicited local adverse reactions following QIV vaccination compared corresponding local adverse reactions after TIV vaccination. The frequencies of solicited adverse events were modestly higher in younger subjects compared to older children and adults. No deaths occurred in Study V130_03, and none of the 12 deaths in Study V130_01 were related to Flucelvax QIV vaccination. The safety profile for the Flucelvax QIV was consistent with the safety profile of other licensed inactivated seasonal QIV's.

Pediatric Research Equity Act
In accordance with the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), the requirement for studies in children from birth to <6 months of age was waived because vaccination with Flucelvax QIV in infants <6 months of age would provide no meaningful therapeutic benefit over initiating vaccination at 6 months of age, and Flucelvax QIV is not likely to be used in a substantial number of infants < 6 months of age. A study in children 6 months to <4 years of age was deferred because the product is ready for approval in individuals 4 years of age and older.

Post marketing Actions
The post-marketing requirements include the following studies:
- In accordance with the accelerated approval regulations, a confirmatory clinical endpoint efficacy study (V130_12) will be conducted in children 4 to <18 years of age to verify and further describe the clinical benefit of Flucelvax QIV.

- A safety and immunogenicity study (V130_10) in children 6 months to <4 years of age will be conducted to fulfill PREA requirements.

The applicant's plan for continued monitoring of the safety of Flucelvax QIV by routine pharmacovigilance in the post-marketing period is acceptable.

1.1 Demographic Information: Subgroup Demographics and Analysis
Subgroup demographic analyses are presented in detail in subsections 6.1.11.3 and 6.2.11.3.
In the pediatric study, V130_03: The immune responses to the two A strains, [GMT titers, percentage achieving HI titer≥1:40 and seroconversion rates], were similar between the two age groups [4 years to <9 years and 9 years to <18 years of age]. For the two B strains, comparisons of HI responses between the two age groups indicated that the older age group achieved higher GMT titers and higher percentage of subjects with HI titer ≥1:40, although the seroconversion rates for each of the B strains were both somewhat lower in the older age group. These findings are not explained by the baseline GMT titers and percentage of subjects with HI titers≥1:10 which were very similar for the two age groups [see table 3.1.5-3 in the ISE p.32]. Per ACIP recommendations, children ages 4-9 years who were not previously vaccinated received two doses of influenza vaccine and there were 694 not previously vaccinated subjects in this age group as compared to 468 who were previously vaccinated [Table 2.1, CSR V130_03, p.28]. In this reviewer's opinion these differences in GMT titers and percentage achieving HI titer≥1:40 as a function of younger age are not likely to be clinically significant.
Sex differences: There were no significant differences in HI responses between males and females for any of the four strains, by GMT titers, HI titers ≥1:40 or seroconversion rates [data not shown].
Race/ethnicity differences: There were no significant differences based on three race/ethnic subgroups (black, Caucasian, Hispanic) for any of the four strains, as measured by GMT titers, HI titers ≥1:40 or seroconversion rates [data not shown].

In the adult study, V130_01: Age differences: the GMT titers obtained at three weeks post-vaccination were consistently higher in the age group 18 to <65 years compared to the age group ≥65 years. The data are consistent with the immunogenicity of influenza vaccines reported in the published literature, and, in this reviewer's opinion, probably clinically significant in that influenza infection rates are generally higher in elderly adults.
Sex differences: Table 3.3.2-1 in the Integrated Summary of Efficacy [ISE], p.47 summarizes the differences in HI responses by sex as measured by GMT titers, percentage of subjects with HI antibody titers ≥1:40 and seroconversion rates. There was no significant difference by sex of subject for any of these parameters.

Race/Ethnicity: In general, HI responses were higher in blacks than Hispanics, and whites had the lowest immune responses of the three groups. This pattern was evident for GMT titers and for seroconversion rates, but not for the percentage of subjects achieving HI titers ≥1:40. This pattern is consistent for all four strains.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Influenza, a respiratory and systemic illness caused by influenza virus infection, is an important cause of infectious morbidity and mortality worldwide. Annual influenza epidemics are responsible for an estimated 3 to 5 million cases of severe respiratory illness, and about 250,000 to 500,000 deaths worldwide each year [Ref. 1]. In the United States, an estimated 55,000 to 431,000 hospitalizations [Ref.2] and 3,000 to 49,000 deaths [Ref.3] are attributed to influenza each year. Influenza causes morbidity in all ages, with the highest attack rates in children, and the highest rates of serious morbidity and death among the elderly (who account for 90% of influenza-attributable deaths in the US), infants and young children, and persons with specific underlying medical conditions, such as chronic pulmonary or cardiac disease [Ref.4].

Influenza viruses are single, negative-stranded RNA viruses of the Orthomyxoviridae family. Humans are primarily affected by two influenza virus types, A and B. Influenza A viruses are further categorized into subtypes based upon their two primary surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA). Type B influenza viruses are comprised of a single HA and NA subtype. Generally, one strain from a specific type or subtype is the predominant circulating virus, while representative strains from the other two groups co-circulate at lower rates. Each year, global surveillance data are reviewed to predict which strains are likely to circulate in the following influenza season, and three are chosen for inclusion in the vaccine. Methods for predicting the next season's circulating strains are not always successful, and years in which the vaccine strains are not well matched to the season's strains continue to occur.

Two antigenically distinct B virus lineages, known as B/Victoria and B/Yamagata, have alternated in circulation. Since 2001, the two lineages have co-circulated during each influenza season in the United States, usually with one lineage predominating over the other in most seasons [Ref.5]. Public health agencies have only been able to predict the prevailing B lineage roughly half of the time. Even during seasons in which the vaccine is matched to the more common lineage, B viruses of the alternate lineage can still represent a significant minority of circulating strains.

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

Prevention of influenza infection may be achieved through avoidance of contact with infectious respiratory droplets by the use of face masks, hand washing, and limiting contact with infected persons, vaccination (trivalent and quadrivalent influenza vaccines) and use of antiviral medication.

There are two classes of antiviral drugs, the adamantines and the neuraminidase inhibitors, that have been approved for both treatment and prevention (pre-exposure chemoprophylaxis) of influenza infection. Widespread resistance to the adamantine class has resulted in a situation where only the neuraminidase inhibitors are currently effective against most seasonal influenza viruses, although resistance to drugs in this class has developed sporadically.

2.3 Safety and Efficacy of Pharmacologically Related Products

There are currently 14 seasonal influenza vaccines (10 trivalent, 4 quadrivalent,) that are licensed in the U.S. Two of the vaccines are live, attenuated; two are cell-based, inactivated vaccines; 12 are egg-based inactivated vaccines. There is one high-dose formulation and one adjuvanted vaccine for use in elderly adults who traditionally did not respond as robustly to standard dose formulations. Each of these licensed influenza vaccines have the indication for the prevention of influenza infection for the strains contained in the vaccine and each has an acceptable safety profile.

In general, the most common solicited adverse events reported following influenza vaccination are injection site pain, headache, fatigue and myalgia. Hypersensitivity reactions, including anaphylaxis, are uncommon. Syncope (fainting) can occur in association with administration of injectable vaccines, including Flucelvax. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements.

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

Flucelvax trivalent formulation has been licensed in the U.S. since 2012. Routine pharmacovigilance has not revealed any new safety signals.

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

The final recommendations for this clinical review were dictated by the following regulatory activities:

1. IND 15744, amendment 0: Following review of the protocol for study V13_03, CBER advised the applicant that use of Flucelvax TIV would not be adequate as

a comparator vaccine in non-inferiority analyses of HI antibody responses, which is an approach that can be used to infer effectiveness of Flucelvax QIV using the traditional approval pathway, unless Flucelvax TIV was licensed in the US in children 4 to <18 years of age. At the time the study was conducted, Flucelvax TIV was not approved by the FDA for use in children 4 to <18 years of age.

2. STN #125408\101 (Flucelvax [TIV] vaccine for use in children 4 to <18 years of age):
a. Following review of the safety and immunogenicity data, a Complete Response [CR] letter was issued 17-September-2015. The CR letter informed the applicant that: "The data contained in your supplement do not support the effectiveness of Flucelvax (TIV) in persons 4 to <18 years of age. In particular, we note that immunologic non-inferiority of Flucelvax compared to Fluvirin with respect to the A/H3N2 influenza strain contained in your vaccine was not demonstrated in persons 4 to <9 years of age. Furthermore, a finding of lower immune response for the A/H3N2 strain was also apparent in the descriptive immunogenicity data in subjects 9 to <18 years of age." The result of that CR letter is that Flucelvax TIV is not currently a U.S. licensed vaccine and therefore the results from Study V130_03 in children ages 4 to <18 years, that used Flucelvax TIV as the comparator vaccine, cannot be accepted in support of a traditional approval pathway for this age range for Flucelvax QIV.

b. Alternative pathways for licensure for the pediatric age indication of 4 to <18 years for both Flucelvax TIV and Flucelvax QIV were discussed with the applicant in a Type A meeting on 29-October-2015. FDA advised the applicant that the Flucelvax QIV immunogenicity data in individuals 4 to <18 years of age might support approval via the accelerated approval (AA) pathway. For additional details, please see sections 11.3 and 11.4 of this clinical review (STN #125408\127).

3. STN #125408\127 (Flucelvax QIV), amendment submitted January 2016: The applicant submitted a request for AA approval of QIV (concurrent request submitted to STN #125408\101) in ages 4years to <18 years. The basis for considering the AA pathway is described in the FDA Guidance for Industry "Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines", in children 4 to <18 years of age. HI antibody represented a biological marker that is reasonably likely to predict clinical benefit. In accordance with the accelerated approval regulations, a confirmatory clinical endpoint efficacy study (V130_12) will be conducted in children 4 to <18 years of age to verify and further describe the clinical benefit of Flucelvax QIV.

2.6 Other Relevant Background Information

N.A.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized to accommodate a complete clinical review.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The studies submitted in this supplemental application were conducted in accordance with Good Clinical Practice. All study sites were in the U.S. There were no significant issues identified by the CBER BIMO inspections. Please refer to the CBER BIMO review memo for details.

3.3 Financial Disclosures

Covered clinical study (name and/or number):		
Was a list of clinical investigators provided:	Yes X ☐	No ☐ (Request list from applicant)
Total number of investigators identified: 1,051		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Insert text here

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

4.1 Chemistry, Manufacturing, and Controls

There were no issues identified by the CBER CMC reviewer that would impact the clinical review considerations.

4.2 Assay Validation

There were not significant issues with the assays identified by the CBER assay reviewer that would impact the clinical review considerations.

4.3 Nonclinical Pharmacology/Toxicology

N.A.

4.4 Clinical Pharmacology

N.A.

4.4.1 Mechanism of Action

The mechanism of action of influenza vaccines is related mostly to the induction of hemagglutination inhibition antibodies. Although specific levels of antibody have not been absolutely correlated with protection from influenza illness, HI antibody titers of ≥ 1:40 have been associated with protection from influenza illness in up to 50% of subjects in some studies [Ref. 6].

4.4.2 Human Pharmacodynamics (PD)

N.A.

4.4.3 Human Pharmacokinetics (PK)

N.A.

4.5 Statistical

Please refer to Section 6.1.9.

4.6 Pharmacovigilance

There were no significant issues identified by the CBER OBE reviewer that would impact the clinical review considerations.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

This review is based upon the data submitted for two Phase 3 clinical trials, V130_03 in children 4-18 years of age and V130_01 in adults 18 years and older. The two trials had identical co-primary and secondary immunogenicity endpoints.

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

The clinical study reports, pertinent case report tabulations and forms, labeling, financial information, clinical overview, pediatric study plan/requests for partial waiver, and clinical summaries, applicant responses to clinical information requests were reviewed. In addition, amendments to the supplement (128 to 135) that were received by CBER after the submission of this efficacy supplement STN 125408.127 were also reviewed.

5.3 Table of Studies/Clinical Trials

Table 1 lists the clinical trials that were reviewed for this sBLA submission.

Table 1. Clinical Trials for Flucelvax Quadrivalent Efficacy Supplement

Study No./country/start and end date	Study description	Population	Treatment Assignment	Number of Subjects
V130_03	Phase 3,	4-18 years	4-9 years	
U.S.	randomized,		QIVc	235
Nov.7.2013	controlled,		TIVc1	120
Aug. 19,2014	multi-center,		TIVc2	113
	one or two		9-18 years	
	doses		QIVc	584
	depending on		TIV1c	300
	prior influenza		TIV2c	287
	vaccination*		Total	2,333
V130_01	Phase 3,	18 years and	18-65 years	
U.S.	randomized,	older	QIVC	674
Nov.14, 2013	controlled,		TIVc1	334
July 11,2014	multi-center,		TIVc2	332
	single dose		>65 years	
			QIVc	661
			TIVc1	342
			TIVc2	337

Total	2,680

Source: Adopted from Complete Study Report [CSR] V130_03, p.7 and CSR V130_01, p.6.
*number of doses received per Advisory Committee on Immunization Practices (ACIP) recommendations.

5.4 Consultations

N.A.

5.4.1 Advisory Committee Meeting (if applicable)

N.A.

5.4.2 External Consults/Collaborations

N.A.

5.5 Literature Reviewed (if applicable)

1. WHO. WHO/Europe influenza surveillance. Available at: http://www.euroflu.org/index.php. Accessed April 12, 2012.
2. WHO. WHO/Europe influenza surveillance. Available at: http://www.euroflu.org/index.php. Accessed April 12, 2012.
3. CDC. Influenza Associated Pediatric Deaths - United States, September 2010-August, 2011. MMWR 2011; 60:1233-38.
4. CDC (US Centers for Disease Control and Prevention). Seasonal influenza activity surveillance reports: 1999- 2000 to 2012-2013 seasons. Available at: http://www.cdc.gov/flu/weekly/pastreports.htm. Accessed April 10, 2013.
5. WHO. Recommended composition of influenza virus vaccines for use in the 2012-2013 northern hemisphere influenza season. Available at:http://www.who.int/influenza/vaccines/virus/recommendations/2013_14_north/en/index.html Accessed April 10, 2013.
6. Feigin RD, Cherry JD, Demmler-Harrison GJ, Kaplan SL. Textbook of Pediatric Infectious Diseases. 6th [2], 2402-2403. 2009. Philadelphia, Saunders Elsevier.1.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Study: V130_03: A Phase III, Stratified, Randomized, Double-Blind, Multicenter, Non-Inferiority Study to Evaluate Safety and Immunogenicity of Cell-Based Quadrivalent Subunit Influenza Virus Vaccine and Cell-Based Trivalent Subunit Influenza Virus Vaccines in Subjects Ages ≥4 Years to <18 Years.

6.1.1 Objectives (Primary, Secondary, etc)

Primary: Immunogenicity
1. To demonstrate non-inferiority of antibody responses of Quadrivalent Subunit Influenza Virus Vaccine (QIVc; Flucelvax QIV) to comparator Trivalent Subunit Influenza Virus Vaccine (TIV1c; Flucelvax TIV) in subjects 4 to <18 years of age, as assessed by the ratio of geometric mean titer (GMT) for each of the 4 vaccine strains separately after vaccination.
2. To demonstrate non-inferiority of antibody responses of QIVc to comparator TIV1c after vaccination in subjects 4 to <18 years of age, as assessed by differences in seroconversion rates for each of the 4 vaccine strains separately after vaccination. Seroconversion is defined in subjects seronegative at baseline (HI titer <1:10 at day 1) as post vaccination HI titer ≥1:40, and defined in subjects seropositive at baseline (HI titer ≥1:10 at day 1) as a minimum of a 4-fold increase in post vaccination HI titer.

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

The vaccine composition of TIV1c and QIVc are described in section 6.1.4 of this review.

Secondary: Immunogenicity
1. To evaluate the antibody responses to all 4 influenza vaccine strains after vaccination according to the Center for Biologics Evaluation, Research and Review (CBER) criteria as follows: The upper bound of the two-sided 95% CI on the ratio of the GMTs (GMT U.S. licensed vaccine/GMT new vaccine) should not exceed 1.5; The upper bound of the two-sided 95% CI on the difference between the seroconversion rates (Seroconversion U.S. licensed vaccine - Seroconversion new vaccine) should not exceed 10%. [Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines, May 2007, p.10]
2. To evaluate the antibody responses to all 4 influenza vaccine strains after vaccination according to Committee for Medicinal Products for Human Use (CHMP) criteria.
3. To demonstrate superiority of antibody responses of the first B strain (B1) in QIVc as compared to TIV2c (containing the B2 strain) as assessed by GMT ratios and seroconversion rates. The upper bound of the 2-sided 95% CI for the ratio of GMTs (GMT TIV2c /GMT QIVc) for HI antibody should not exceed the non-inferiority margin of 1.5
4. To demonstrate superiority of antibody responses of the second B strain (B2) in QIVc as compared to TIV1c (containing the B1 strain) as assessed by GMT ratios and seroconversion rates. The upper bound of the 2-sided 95% CI for

the ratio of GMTs (GMT TIV1c /GMT QIVc) for HI antibody should not exceed the non-inferiority margin of 1.5.

6.1.2 Design Overview

This was a phase 3, randomized, double-blind, multicenter, non-inferiority study to evaluate the immunogenicity and safety of QIVc, TIV1c, and TIV2c in subjects ≥4 to <18 years of age. QIVc was compared to the influenza strains contained in two trivalent inactivated influenza vaccines produced using the same cell-based manufacturing process: TIV1c as constructed to match the WHO's recommended influenza strains for the 2013/2014 season, and TIV2c, an influenza vaccine containing the same influenza A strains as TIV1c but with the influenza B strain from the alternate lineage ("B2" strain) recommended by the WHO for the composition of QIVc. The data from this study will be used to support the licensure of QIVc in the EU, US, and elsewhere for use in children ≥4 years to <18 years of age.

Reviewer Comment: The study design was reviewed under IND 15744. CBER advised the applicant that
- Immunological non-inferiority of HI antibody responses compared to a US licensed trivalent vaccine (that was FDA-approved for the same age group) is an acceptable approach for demonstrating inferred effectiveness of Flucelvax QIV
- Proceeding with use of Flucelvax TIV as the active comparator vaccine, which was not a licensed vaccine in the U.S. for 4 to <18 years of age, would be at their risk that the immunogenicity data from this study might not support traditional approval of Flucelvax QIV for individuals 4 to <18 years of age.

6.1.3 Population

The study enrolled generally healthy subjects male or female ≥4 years to <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. Informed consent was obtained from a parent or legal guardian and assent was obtained if according to local regulations that was required. The exclusion criteria were the following:

1. Individuals with body temperature measurement ≥38°C (≥100.4°F) within 3 days prior to vaccination.
2. Individual who (aside from elevated body temperature) otherwise has a chronic or acute illness that, in the opinion of the investigator, would interfere with the subject's safety during study participation.
3. Any individual who (aside from elevated body temperature) otherwise has a chronic or acute illness that, in the opinion of the investigator, would interfere with

the subject's with the subject's compliance with study related procedures and/or could interfere with the evaluation of study vaccine.
4. If the individual is female, “of childbearing potential”, sexually active, and has not used any of the “acceptable contraceptive methods” for at least 2 months prior to study entry and through day 60.
5. Individual is a female of childbearing potential with a positive or indeterminate pregnancy test.
6. Individual is a pregnant or breast-feeding female.
7. Individual and/or individual’s parents/guardians who were not able to comprehend or follow all required study procedures for the whole period of the study.
8. Individuals with known history of Guillain-Barré Syndrome.
9. Current alcohol abuse or drug addiction.
10. Individuals with a diagnosis of any bleeding disorder that represents a contraindication to IM vaccination and blood draws.
11. Individuals with a known history of any anaphylaxis, serious vaccine reactions, or hypersensitivity to any of the vaccine components described in the IB.
12. Individuals with a known anaphylaxis or severe hypersensitivity reaction following exposure to latex.
13. Individual has participated in any clinical trial with another investigational product 30 days prior to first study visit or intent to participate in another clinical study at any time during the conduct of this study. Concomitant participation in an observational study (not involving drugs, vaccines, or medical devices) is acceptable.
14. Individual has received influenza vaccination or has had documented influenza disease within the past 6 months.
15. Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or systemic corticosteroid therapy (prednisone or equivalent) at any dose for more than 2 consecutive weeks (14 days) within the past 3 months. Topical, inhaled and intranasal corticosteroids are permitted. Intermittent use (one dose in 30 days) of intra-articular corticosteroids is also permitted.
16. Individual who has received blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation in the past 12 weeks.
17. Individuals or children of individuals who are employees of the Investigator or study center, with direct involvement in the proposed study or other studies under the direction of the Investigator or study center, as well as immediate family members of the employees or the Investigator.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The dose and formulation of the study agents are listed in Table 2.

Table 2. Study Vaccine Composition

Vaccine Description	Antigen Name (Dose)	Volume (Route of Administration)	Excipients
QIVc	HA antigens from influenza strains (A/Brisbane/10/2010 [H1N1], A, A/Texas/50/2012 NYMC X-223A [H3N2] B/Massachusetts/02/2012 [B1], B/Brisbane/60/2008 [B2]) (approximately ≥15 µg HA per strain)	Approximately 0.5-mL (IM)	[redacted]
TIV1c	HA antigens from influenza strains A/Brisbane/10/2010 [H1N1], ,A/Texas/50/2012 NYMC X-223A [H3N2] B/Massachusetts/02/2012 [B1) (Approximately ≥15 µg HA per strain)	Approximately 0.5-mL (IM)	[redacted]
TIV2c	HA antigens from influenza strains(A/Brisbane/10/2010 [H1N1], A/Texas/50/2012 NYMC X-223A [H3N2], B/Brisbane/60/2008 [B2]), (Approximately ≥15 µg HA per strain)	Approximately 0.5-mL (IM)	[redacted]

Source: Table 5.1-1, Protocol version 2, dated 06 May 14.
Abbreviations: HA- hemagglutinin, [redacted]

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:
1. Any child 9 years of age and older.
2. 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:
1. 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).
2. Any child under the age of 9 years with unknown influenza vaccination history.
Subjects were to participate in the study through a treatment and follow-up period (up to approximately 6 or 7 months total dependent on stratification).

6.1.5 Directions for Use

Shake the syringe vigorously before administering. Flucelvax QIV should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use the vaccine if the contents have been frozen. Attach a sterile needle to the pre-filled syringe and administer intramuscularly only. Do not administer this product intravenously, intradermally or subcutaneously.

6.1.6 Sites and Centers

Participants were recruited and enrolled from 90 study sites in the U.S. Study was conducted under IND 15744.

6.1.7 Surveillance/Monitoring

Schedule of Events: Table 3 shows the schedule of events by study visit day.

Table 3. Times and Events Table - Previously Vaccinated Subjects

Visit Type	Treatment Period				Follow-up Period		Unscheduled Visit[a]
	Clinic Visit	Reminder Call	Reminder Call	Clinic Visit	Safety Telephone	Clinic Visit	Clinic Visit
Visit Number	**1**	**--**	**--**	**2**	**3[d], 4, 5, 6, 7**	**8**	-
Study Day	**1**	**3**	**5**	**22**	**30[d], 60, 90, 120, 150**	**181**	-
Study Visit Time Window (min-max)	**Not applicable**	**2-4 days post vaccination[c]**	**4-6 days post vaccination[c]**	**20-29 days post vaccination**	**-7/+7 days each call**	**165 – 195 days post vaccination**	**Day 1 through Day 181**
Informed Consent/Assent	X[b]						
Exclusion/Inclusion Criteria	X[b]						
Medical History	X[b]						
Review of Systems[e]	X[b]			X		X	X
Physical Examination[f]	X[b]						
Brief History/Symptom Directed Physical Examination[f]				X		X	X
Pregnancy Test (Only for Females of Childbearing Potential)[g]	X[b]			X		X	
Blood Draw	X[b]			X			
Study Vaccine Administered	X						
30 Minutes Post Injection Assessment (Local and Systemic AEs, AEs, Body	X						
Diary Card Dispensed[i]	X						
Diary Card Completion		X	X				
Diary Card Reviewed and Collected[k]				X			
Scripted Safety Interview					X		
Assess all AEs[l]	X			X	X	X	X
Assess SAEs[m]	X			X	X	X	X

Visit Type	Treatment Period				Follow-up Period		Unscheduled Visit[a]
	Clinic Visit	Reminder Call	Reminder Call	Clinic Visit	Safety Telephone	Clinic Visit	Clinic Visit
Visit Number	**1**	**--**	**--**	**2**	**3[d], 4, 5, 6, 7**	**8**	-
Study Day	**1**	**3**	**5**	**22**	**30[d], 60, 90, 120, 150**	**181**	-
Study Visit Time Window (min-max)	**Not applicable**	**2-4 days post vaccination[c]**	**4-6 days post vaccination[c]**	**20-29 days post vaccination**	**-7/+7 days each call**	**165 – 195 days post vaccination**	**Day 1 through Day 181**
Assess Medically Attended AEs and AEs Leading to Withdrawal from Study, NOCDs[n]	X			X	X	X	X
Assess Influenza-like Symptoms[o]	X			X			X
Concomitant Medications[p]	X			X	X	X	X
Study Termination						X	

Source: Adapted from sBLA 125408.127, CSR for V130_03, Table 2-3, p. 45

6.1.8 Endpoints and Criteria for Study Success

There were two co-primary immunogenicity endpoints:

1. GMT of all 4 influenza strains as measured on day 1, day 22 (“previously vaccinated” subjects) and day 50 (“not previously vaccinated” subjects).Criteria for success was the upper bound of the 2-sided 95% CI for the ratio of GMTs (GMTTIV1c or TIV2c /GMTQIVc) for HI antibody should not exceed the non-inferiority margin of 1.5

2. Percentages of subjects achieving seroconversion and HI titer ≥1:40 as calculated for all 4 influenza strains on day 1, day 22 (“previously vaccinated” subjects) and day 50 (“not previously vaccinated” subjects).The differences in seroconversion rates for each of the 4 vaccine strains separately after vaccination, criteria for success, was 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 non-inferiority endpoints met the success criteria.

There were three secondary immunogenicity objectives:

1. To evaluate the antibody responses to all 4 influenza vaccine strains after vaccination in the age cohorts: ≥4 to ≤18 years according to the Committee for Medicinal Products for Human Use (CHMP) criteria [CHMP, 1997].

2. To demonstrate superiority of antibody responses to the first B strain (B1) in QIVc as compared to TIV2c (containing the B2 strain) as assessed by GMT ratios and seroconversion2 rates in children ≥4 years of age and ≤18 years of age. Criteria for success was the upper bound of the 2-sided 95% CI for the ratio of GMTs (GMT TIV2c /GMT QIVc) for HI antibody should not exceed the superiority margin of 1.5; the lower bound of the 2-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody should meet or exceed 40%. The lower bound of the 2-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥1:40 should meet or exceed 70%.

3. To demonstrate superiority of antibody responses to the second B strain (B2) in QIVc as compared to TIV1c (containing the B1 strain) as assessed by GMT ratios and seroconversion2 rates in children ≥4 years of age and ≤18 years of age. Criteria for success was the upper bound of the 2-sided 95% CI for the ratio of GMTs (GMT TIV1c /GMT QIVc) for HI antibody should not exceed the superiority margin of 1.5; the lower bound of the 2-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody should meet or exceed 40%. The lower bound of the 2-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥1:40 should meet or exceed 70%.

<u>Reviewer Comment:</u> The success criteria for each of the co-primary and secondary endpoints were appropriate for the stated study objectives and sufficient to support the hypotheses that the GMTs achieved after administration of Flucelvax QIV were non-inferior to those of Flucelvax TIV for the two A strains and the first B strain; and that the GMTs to the second B strain [B2] in the QIV formulation were superior to those of the first B strain [B1] in the TIV formulation.

There were Study Protocol amendments and SAP amendments as described below.

Protocol Amendment:
The original study protocol was issued on June 21, 2013. The protocol was amended and reissued on May 06, 2014 and incorporated some administrative changes: (1) inclusion of safety analysis based on age groups and time periods as detailed in SAP. (2) clarification regarding clinic visit and safety call visit windows.(3) correction of how the IRT system assigns Subject Identifiers.(4) correction of sequence for enrollment and randomization.(5) clarification on use of diary cards assigned to subject based on age at time of enrollment.

SAP amendments:
An amendment 1 to the Analysis Plan version 1 dated November 04, 2013 was issued on May 14, 2014 and incorporated following changes: (1) an error in the definition of FAS population was rectified (2) a subgroup for solicited and

unsolicited AEs analysis was added (3) the statistical methods for primary objective were rephrased for clarity and correctness (4) text was added to adjustment of covariates on model to be used on subgroup analysis. (5) type 2 analysis of solicited AEs and analysis of temperatures increments was removed and (6) a reference for Miettinen Nurminen Mee method was added.

Amendment 2 was issued on August 28, 2014 included following changes: (1) the data set was analyzed for all vaccines and all strains. (2) unsolicited safety set for all analysis periods was added (3) additional subgroup analysis with or without the preventive use of analgesics/antipyretics was added (4) definition for subgroup variable race/ethnicity was included.

Amendment 3 was issued on October 01, 2014 included following changes: (1) overall solicited safety set (local, systemic and other reactions) was included (2) analysis adapted to account for the sparse data (too little observations per vaccine group/center).

Reviewer Comment: The Study Protocol and SAP amendments did not affect the analysis of the study objectives in any manner that would substantively impact the clinical reviewer's summary or recommendations.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Please refer to the statistical review for details concerning the Statistical Analysis Plan [SAP].

The sample size for subjects 4 to <18 years of age was calculated to demonstrate that all 8 primary hypotheses (NI in terms of GMT and seroconversion) will be rejected with an overall power of approximately 86% and a 1-sided α=0.025, assuming independence. Assuming a drop-out rate and exclusions from PPS of approximately 15%, 1176 subjects in QIVc arm and 588 in each of the TIV1c and TIV2c arm were to be enrolled.

No data were imputed. Missing data per subject were identified and data analysis was accomplished per protocol. The primary analyses were based on the immunogenicity PPS. The applicant also provided additional analyses based on the immunogenicity FAS.

The FAS (overall and for each influenza vaccine strain) consisted of all subjects in the enrolled population who received the study vaccination and provided immunogenicity data at the day(s) of baseline (prior to first vaccination) and 3 weeks after the (last) vaccination. The FAS populations were analyzed "as randomized".

The PPS included all subjects in FAS who received the study vaccine(s) according to the treatment assignment, had no major protocol deviations, and were not excluded from the study for reasons such as withdrawal of consent or influenza-like illness.

Separate PPSs were defined according to study objective and/or time point (i.e., Analyses of the primary objectives might not be based on the same subjects).

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Table 4 lists the numbers of subjects who were enrolled, exposed and completed the study.

Table 4. Summary of All Enrolled Set[1]

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%)

Source: Adapted from sBLA 125408.127, CSR for V130_03, Table 14.1.1.2, p. 99
Abbreviation: AE, adverse event.
[1]All Enrolled Set includes all subjects who were enrolled in the study and randomized.

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.

Reviewer Comment: All enrolled subjects were vaccinated and 94% of subjects in each treatment completed the study. There were no significant imbalances between groups in the rates of premature withdrawals and lost to follow up. In this reviewer's opinion, the results of the study are not biased by imbalance in

proportion of subjects between groups on variables that could affect the validity of the study results.

6.1.10.1.1 Demographics
The demographic profile of the subjects in Study V130_03 is presented in Table 5.

Table 5. Demographic and Baseline Characteristics - All Enrolled Set

Vaccine Group	**QIVc**	**TIV1c**	**TIV2c**
	N=1159	N=593	N=581
Age (years)	9.5±3.8	9.5±3.8	9.3±3.7
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 N=592	139.0±21.39 N=578
Weight (kg) ±SD	40.82±21.95	40.64±20.69 N=592	40.40±20.97 N=578
Body Mass Index (kg/m^2) ±SD	19.6±5.34	19.6±5.26 N=592	19.6±5.76 N=578
R**ace/Ethnic:**			
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%)
Met entry criteria			
Yes	1158 (100%)	593 (100%)	580 (100%)
Previous influenza Vaccination			
Yes	819 (71%)	420 (71%)	400 (69%)

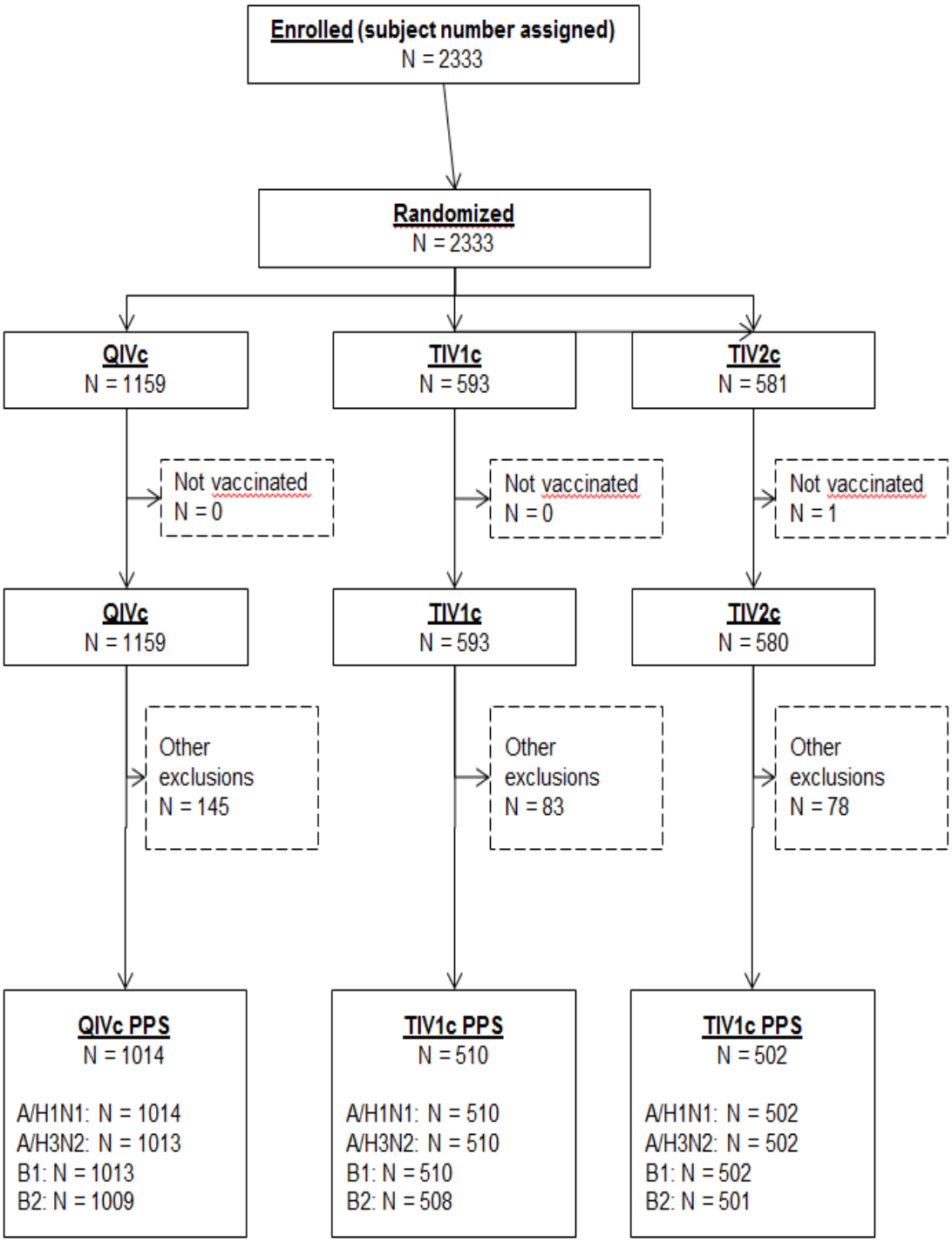
Source: Adapted from sBLA 125408.127, CSR for V130_03, Table 11.2-1, p. 106.

<u>Reviewer Comment:</u> The demographic characteristics of the study populations do not vary by treatment group and generally reflect the racial/ethnic composition of the U.S. population. There are slightly more males than females in the study however in this reviewer's opinion the difference is not clinically significant. The percentage of subjects who were previously vaccinated is similar between treatment groups.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
The most significant characteristic of the enrolled population that could have biased the results of the study, on the immunogenicity endpoints, is the status of the subject with regards to previous influenza vaccination. This characteristic was well-balanced between all three treatment groups [see Table 4 in section 6.1.10.1.1] and therefore this potential bias was handled by the enrollment process.

6.1.10.1.3 Subject Disposition
A flow chart of subject disposition is presented in Figure 1.

Figure 1. Subject Disposition Flowchart



Source: Adapted from sBLA 125408.127, CSR for V130_03, p.110

6.1.11 Efficacy Analyses

The results for the co-primary endpoints are presented in subsection 6.1.11.1. The results for the secondary endpoints are presented in subsection 6.1.11.2.

6.1.11.1 Analyses of Primary Endpoint(s)

Analyses of the primary endpoints are presented in Tables 6 and 7.

Table 6. Geometric Mean Titer (95% CI), and Vaccine Group Ratios (95% CI), 3 Weeks After Last Vaccination, HI Assay-Per Protocol Set

	QIVc	TIV1c or TIV2c[a]	Vaccine Group Ratio
H1N1	N=1014	N=510	
TIVDay 22 or day 50[b]	1090 (1027-1157)	1125 (1034-1224)	**1.03** (0.93-1.14)
H3N2	N=1013	N=510	
Day 22 or day 50 [b]	738 (703-774)	776 (725-831)	**1.05** (0.97-1.14)
B1	N=1013	N=510	
Day 22 or day 50 [b]	155 (146-165)	154 (141-168)	**0.99** (0.89-1.1)
B2	N=1009	N=501	
Day 22 or day 50 [b]	185 (171-200)	185 (166-207)	**1.00** (0.87-1.14)

Source: Adapted from sBLA 125408.127, CSR for V130_03, Table 2-4, p.28
Abbreviations: CI-confidence interval, HI-hemagglutination-inhibition
[a] For H1N1, H3N2 and B1 influenza strain ratio of GMTs was calculated as TIV1c/QIVc, whereas for B2 influenza strain ratio of GMTs was calculated as TIV2c/QIVc.
[b] Analysis is performed on day 22 for previously vaccinated subjects and day 50 for not previously vaccinated subjects.
The non-inferiority criteria were met: The upper bound of the 2-sided 95% CI for the ratio of GMTs (GMT_{TIV1c} or $_{TIV2c}$ /GMT_{QIVc}) for HI antibody was less than 1.5.

Table 7. Number (%) of Subjects with Seroconversion (95% CI) and Vaccine Group Difference (95% CI), 3 Weeks After Last Vaccination, HI Assay – Per Protocol Set

	QIVc	TIV1c orTIV2c[a]	Vaccine group Difference
H1N1	N=1014	N=510	
Day 22 or day 50[b]	732 (72%) (69%-75%)	380 (75%) (70%-78%)	2% (-2.5%- **6.9%**)
H3N2	N=1013	N=510	
Day 22 or day 50 [b]	473 (47%) (44%-50%)	258 (51%) (46%-55%)	4% (-1.4%- **9.2**%)
B1	N=1013	N=510	
Day 22 or day 50 [b]	672 (66%) (63%-69%)	336 (66%) (62%-70%)	0% (-5.5%- **4.5**%)
B2	N=1009	N=501	
Day 22 or day 50 [b]	735 (73%) (70%-76%)	357 (71%) (67%-75%)	-2% (-6.5%- **3.2**%)

Source: Adapted from sBLA 125408.127, CSR for V130_03, Table 2-5, p.29
Abbreviations: CI-confidence interval, HI-hemagglutination-inhibition
[a] For H1N1, H3N2 and B1 influenza strain, the ratio of seroconversion and vaccine group difference was calculated as TIV1c/QIVc; for the B2 influenza strain, the ratio of seroconversion and vaccine group difference was calculated as TIV2c/QIVc.
[b] Analysis was performed on day 22 for previously vaccinated subjects and on day 50 for not previously vaccinated subjects.

Results: The non-inferiority criteria were met: The upper bound of the 2-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV1c or TIV2c – % seroconversion QIVc) for HI antibody was less than 10%.

> *Reviewer Comment: The data in Tables 6 and 7 indicate that there is no interference observed in the immune responses to the two A strains and the first B strain following Flucelvax quadrivalent vaccination compared to the trivalent formulation, and in addition Flucelvax vaccination induces HI antibody responses to the second B strain no inferior to the single B strain in TIV. Depending upon the circulating strains in any particular year, there may be additional clinical protection from acute influenza infection afforded by the second B strain immune responses.*

6.1.11.2 Analyses of Secondary Endpoints

The CBER Guidance criteria for seroconversion and for the percentage of subjects achieving HI titers ≥1:40, 3 weeks after vaccination, were met following QIVc, TIV1c and TIV2c vaccination, respectively (Table 8).

Table 8. Number (%) of Subjects with Seroconversion and HI Titer ≥1:40 (95% CI), 3 Weeks After the Last Vaccination, HI Assay - Full Analysis Set

	QIVc	TIV1c/or/TIV2c[a]
H1N1 Seroconversion	N=1113	N=566
Day 22 or day 50[b]	812 (73%) (**70%-**76%)	417 (74%) (70%-77%)
HI titer ≥1:40	N=1113	N=566
Day 22 or day 50 [b]	1104 (99%) (**98%-**100%)	563 (99%) (98%-100%)
H3N2 Seroconversion	N=1112	N=566
Day 22 or day 50 [b]	527 (47%) (**44%-**50**%)**	287 (51%) (47%-55%)
HI titer ≥1:40	N=1112	N=566
Day 22 or day 50 [b]	1109 (100%) (**99%**-100%)	563 (99%) (98%-100%)
B1 Seroconversion	N=1112	N=566
Day 22 or day 50 [b]	743 (67%) (**64%-**70%)	371 (66%) (61%-69%)
HI titer ≥1:40	N=1112	N=566
Day 22 or day 50 [b]	1028 (92%) (**91%**-94%)	525 (93%) (90%-95%)
B2 Seroconversion	N=1108	N=556
Day 22 or day 50 [b]	809 (73%) (**70%**-76%)	401 (72%) (68%-76%)
HI titer ≥1:40	N=1108	N=556
Day 22 or day 50 [b]	1009 (91%) (**89%**-93%)	504 (91%) (88%-93%)

Source: Adapted from sBLA 125408.127, CSR for V130_03, Table11.4.1-3, p.110

[a] For H1N1, H3N2 and B1 influenza strains TIV1c data is presented, whereas for B2 influenza strain TIV2c data is presented.

[b] Analysis was performed on day 22 for previously vaccinated subjects and on day 50 for not previously vaccinated subjects.

Results**:** CBER immunogenicity criteria were met: The percentage of subjects achieving seroconversion for HI antibody was ≥40%. The lower bound of the 2-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥1:40 was >70%.

The second of the secondary objectives for Study V130_03 was to demonstrate superiority of antibody responses to the first influenza B strain (B1) in QIVc as compared to TIV2c (containing the alternative influenza B (B2) strain) and the second B influenza strain (B2) in QIVc as compared to TIV1c (containing the B1

influenza strain) as assessed by GMT ratios and sero-conversion rates in subjects ≥4 to <18 years of age. Tables 9-12 present that data.

Table 9. Geometric Mean Titer and Ratios (95% CI), Against B1 Strain, 3 Weeks After the Last Vaccination, HI Assay – Full Analysis Set

	QIVc	TIV2c	Vaccine Group ratios
	N=1112	N=557	
Day 22 or day 50[a]	154 (145-163)	59 (54-64)	0.38 (0.35-**0.42**)

Source: Adapted from sBLA 125408.127, CSR for V130_03, Table 11.4.1-7, p.114.
[a] Analysis is performed on day 22 for previously vaccinated subjects and day 50 for not previously vaccinated subjects.

Results: Met superiority criteria: The upper bound of the 2-sided 95% CI for the ratio of GMTs (GMT TIV1c or TIV2c /GMT QIVc) for HI antibody did not exceed the superiority margin of 1.0

Table 10. Number (%) of Subjects with Seroconversion (95%CI) Against B1 Strain, 3 Weeks After the Last Vaccination, HI Assay - Full Analysis Set

	QIVc	TIV2c	Vaccine Group Difference
	N=1112	N=557	
Day 22 or day 50[a]	743 (67%) (64%-70%)	182 (33%) (29%-37%)	-34% (-38.8%, **-29.3**%)

Source: Adapted from sBLA 125408.127, CSR for V130_03, Table11.4.1-8, p.114.
[a] Analysis is performed on day 22 for previously vaccinated subjects and on day 50 for not previously vaccinated subjects.

Results: Superiority criteria met: The upper bound of the 2-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV1c or TIV2c – %seroconversion QIVc) for HI antibody did not exceed the margin of 0.

Table 11. Geometric Mean Titer and Ratios (95% CI) Against B2 Strain, HI Assay 3 Weeks After the Last Vaccination - Full Analysis Set

	QIVc	TIV1c	Vaccine Group ratios
	N=1108	N=563	
Day 22 or day 50[a]	176 (164-189)	45 (41-49)	0.25 (0.22-**0.29**)

Source: Adapted from sBLA 125408.127, CSR for V130_03, Table11.4.1-9, p115.
[a] Analysis was performed on day 22 for previously vaccinated subjects and on day 50 for not previously vaccinated subjects.

Results: Met superiority criteria: The upper bound of the 2-sided 95% CI for the ratio of GMTs (GMT TIV1c or TIV2c /GMT QIVc) for HI antibody did not exceed the superiority margin of 1.

Table 12. Number (%) of Subjects with Seroconversion (95%CI) Against B2 Strain 3, Weeks After the Last Vaccination, HI Assay - Full Analysis Set

	QIVc	TIV1c	Vaccine Group Difference
	N=1108	N=563	
Day 22 or Day 50[a]	809 (73%) (70%-76%)	148 (26%) (23%-30%)	-47% (-51.1%, **-42.1%)**

Source: Adapted from sBLA 125408.127, CSR for V130_03, Table11.4.1-10, p115.
[a] Analysis is performed on day 22 for previously vaccinated subjects and on day 50 for not previously vaccinated subjects.

Results: Superiority criteria met: The upper bound of the 2-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV1c or TIV2c – % seroconversion QIVc) for HI antibody did not exceed the margin of 0.

Reviewer Comment: The data indicate that Flucelvax QIVc was immunogenic (inferred effectiveness) against influenza strains contained in the annual vaccine and that no immunological interference with the first B strain or to the two A strains was observed with the addition of a second B strain.

6.1.11.3 Subpopulation Analyses

In this sub-section, analyses stratified by age, sex, race/ethnicity and baseline HI titers are presented in Tables 13-15.

Age differences: Study V130_03 enrolled subjects age 4 years to <18 years. To assess any differences in immunogenicity as a function of age, the results are broken down into two age cohorts, 4-9 years and 9-18 years as shown in Table 13.

Table 13. Immunogenicity Results at 3 Weeks After Last Vaccination in Subjects 4 to < 18 Years of Age, by Age, HI Assay – PPS

		4 to < 9 Years of Age		9 to < 18 Years of Age	
	Day 22/ Day 50[a]	QIVc	TIV1c/or/TIV2c[b]	QIVc	TIV1c/or/TIV2c[b]
A/H1N1	N = 467	N = 238	N = 547	N = 272	
	GMT (95% CI)	1042 (962-1130)	1109 (990-1242)	1139 (1045-1242)	1138 (1007-1286)
	% HI Titer ≥ 1:40 (95% CI)	99% (**98%**-100%)	100% (**98%**-100%)	99% (**98%**-100%)	99% (**97%**-100%)
	Seroconversion Rate[c]	75% (**71%**-79%)	77% (**71%**-82%)	70% (**66%**-74%)	72% (**67%**-78%)

	(95% CI)				
A/H3N2	GMT (95% CI) % HI Titer ≥ 1:40 (95% CI) Seroconversion Rate[c] (95% CI)	N = 467 758 (707-813) 99% (**98%**-100%) 52% (**47%**-56%)	N = 238 782 (709-863) 100% (**98%**-100%) 48% (**42%**-55%)	N = 546 719 (673-767) 100% (**99%**-100%) 42% (38%-47%)	N = 272 762 (694-836) 100% (**98%**-100%) 53% (**46%**-59%)
B1	GMT (95% CI) HI Titer ≥ 1:40 (95% CI) Seroconversion Rate[c] (95% CI)	N = 467 117 (106-128) 89% (**86%**-92%) 71% (**66%**-75%)	N = 238 116 (102-132) 88% (**83%**-92%) 69% (**63%**-75%)	N = 546 200 (185-218) 97% (**95%**-98%) 63% (**58%**-67%)	N = 272 200 (178-224) 97% (**94%**-99%) 63% (**57%**-69%)
B2	GMT (95% CI) HI Titer ≥ 1:40 (95% CI) Seroconversion Rate[c] (95% CI)	N = 464 161 (143-181) 88% (**85%**-91%) 74% (**70%**-78%)	N = 236 166 (141-195) 89% (**85%**-93%) 75% (**69%**-80%)	N = 545 212 (192-235) 95% (**92%**-96%) 72% (**68%**-75%)	N = 265 203 (175-234) 91% (**87%**-94%) 68% (**62%**-74%)

Sources: section 5.3.5.1, 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., pp.160-165
Abbreviations: HI = hemagglutination inhibition. PPS = per protocol set. GMT = geometric mean titer. CI = confidence interval. HI titer ≥ 1:40 = percentage of subjects with HI titer ≥ 1:40.
[a] Day 22 for previously vaccinated subjects, Day 50 for not previously vaccinated subjects.
[b] The comparator vaccine for A/H1N1, A/H3N2 and B1 is TIV1c, for B2 the comparator vaccine is TIV2c.
[c] Seroconversion rate = percentage of subjects with either a pre-vaccination HI titer < 1:10 and post vaccination HI titer ≥ 1:40 or with a pre-vaccination HI titer ≥ 1:10 and a ≥ 4-fold increase in post vaccination HI antibody titer.
Please note that study V130_03 was not formally powered to assess the CBER criteria for immunogenicity in the age subgroups presented in this table.

<u>Reviewer Comment:</u> The immune responses to the two A strains, [GMT titers, percentage achieving HI titer≥1:40 and seroconvesion rates], were similar between the two age groups. However for the two B strains the older age group achieved higher GMT titers and higher percentage of subjects with HI titer ≥1:40, although the seroconversion rates for each of the B strains were both lower in the older age group. These findings are not explained by the baseline GMT titers and percentage of subjects with HI titers ≥1:10 which were similar for the two age

groups[see table 3.1.5-3 in the ISE p.32]. Per ACIP recommendations, children ages 4-9 years who were not previously vaccinated received two doses of influenza vaccine and there were 694 not previously vaccinated subjects in this age group as compared to 468 who were previously vaccinated [Table 2.1, CSR V130_03, p.28]. In this reviewer's opinion, these differences in GMT titers and percentage achieving HI titer ≥1:40 as a function of younger age are not likely to be clinically significant as >85% of the younger children did achieve an HI titer ≥1:40. Table 14, summarizes the HI responses in subjects 4-9 years of age, categorized by vaccination status.

Table 14. Immunogenicity Results of Subjects 4 to < 9 Years of Age, by Previous Vaccination Status, HI Assay – PPS

		4 to < 9 Years of Age Not Previously vaccinated		4 to < 9 Years of Age Previously Vaccinated	
	Day 22/Day 50[a]	QIVc N = 255	TIV1c/TIV2c N = 125/N = 138	QIVc N = 212	TIV1c/TIV2c N = 113/N = 98
A/H1N1	GMT	1063	1165	1011	1065
	(95% CI)	(961-1175)	(1009-1345)	(888-1152)	(891-1274)
	HI Titer ≥ 1:40	100%	100%	99%	100%
	(95% CI)	(98%-100%)	(97%-100%)	(97%-100%)	(97%-100%)
	Seroconversion Rate[b] (95% CI)	80% (75%-85%)	86% (78%-91%)	68% (62%-75%)	67% (58%-76%)
A/H3N2	GMT	865	887	650	676
	(95% CI)	(787-950)	(776-1014)	(592-713)	(595-769)
	HI Titer ≥ 1:40	100%	99%	99%	100%
	(95% CI)	(98%-100%)	(96%-100%)	(97%-100%)	(97%-100%)
	Seroconversion Rate[b] (95% CI)	64% (57%-69%)	61% (52%-69%)	38% (31%-45%)	35% (26%-44%)
B1	GMT	119	141	114	94
	(95% CI)	(106-134)	(119-166)	(98-132)	(77-115)
	HI Titer ≥ 1:40	91%	90%	87%	85%
	(95% CI)	(86%-94%)	(84%-95%)	(81%-91%)	(77%-91%)
	Seroconversion Rate[b] (95% CI)	77% (71%-82%)	74% (66%-82%)	63% (56%-70%)	63% (53%-72%)
B2	GMT	170	197	151 (125-181)	129
	(95% CI)	(147-197)	(161-241)	N = 209	(99-169)

HI Titer ≥ 1:40 (95% CI)	87% (82%-91%)	93% (87%-96%)	89% (84%-93%) N = 209	85% (76%-91%)
Seroconversion Rate[a] (95% CI)	78% (72%-83%)	78% (70%-85%)	70% (64%-76%) N = 209	69% (59%-78%)

Sources: section 5.3.5.1, CSR V130_03 Table 14.2.1.1.7, Table 14.2.1.1.7.1, Table 14.2.1.2.7, Table 14.2.1.2.7.1, Table 14.2.1.3.7 and Table 14.2.1.3.7.1., pp.373-79

Abbreviations: HI = hemagglutination inhibition. PPS = per protocol set. GMT = geometric mean titer. CI = confidence interval. HI titer ≥ 1:40 = percentage of subjects with HI titer ≥ 1:40.

[a] Day 22 for subjects 4 to < 9 years of age "previously vaccinated" and subjects 9 to < 18 years of age, Day 50 for subjects 4 to < 9 years of age "not previously vaccinated".

[b] Seroconversion rate = percentage of subjects with either a prevaccination HI titer < 1:10 and postvaccination HI titer ≥ 1:40 or with a prevaccination HI titer ≥ 1:10 and a minimum 4-fold increase in postvaccination HI antibody titer.

Bold: CBER criterion met. Please note that study V130_03 was not formally powered to assess the CBER criteria for immunogenicity in the age subgroups presented in this table.

Reviewer Comment: For the A/H1N1 strain the GMT titers are similar between previously vaccinated and not previously vaccinated subjects, and 99% or greater of subjects achieved HI titers≥1:40. For A/H3N2 strain there were modestly higher GMT titers in the not previously vaccinated group and 99% or greater of subjects achieved HI titers≥1:40. For the B1 strain GMT titers were similar between the two groups but approximately 5% more subjects in the not previously vaccinated group achieved HI titers≥1:40 as compared to the previously vaccinated group. Finally, for the B2 strain the GMT titers were modestly higher in the not previously vaccinated group and for those subjects who received TIV1c/TIV2c there were 8% more subjects who achieved HI titers≥1:40 in the not previously vaccinated group. In this reviewer's opinion none of these findings are likely to be clinically significant.

Sex differences:

There were no significant differences between males and females for any of the four strains by GMT titers, HI titers ≥1:40 or seroconversion rates [data not shown].

Race/ethnicity differences:
There were no significant differences based on three race/ethnic subgroups (black, Caucasian, Hispanic) for any of the four strains, as measured by GMT titers, HI titers ≥1:40 or seroconversion rates [data not shown].

Baseline HI titer differences:
Table 15 presents the differences in immune responses by baseline HI antibody titers of either ≥1:10 or ≤1:10.

Table 15. Immunogenicity Results of Subjects 4 to < 18 Years of Age by Baseline Immune Status, HI Assay – PPS

		HI Titers < 1:10		HI Titers ≥ 1:10	
	Day 22/Day 50[a]	QIVc	TIV1c/TIV2c[b]	QIVc	TIV1c/TIV2c[b]
A/H1N1		N = 176	N = 77	N = 838	N = 433
	GMT (95% CI)	496 (405-607)	378 (279-514)	1281 (1210-1357)	1385 (1278-1501)
	HI Titer ≥ 1:40 (95% CI)	96% (92%-98%)	99% (93%-100%)	100% (99%-100%)	100% (99%-100%)
	Seroconversion Rate[c] (95% CI)	96% (92%-98%)	99% (93%-100%)	67% (64%-70%)	70% (66%-74%)
A/H3N2		N = 65	N = 33	N = 948	N = 477
	GMT (95% CI)	250 (191-329)	238 (163-350)	791 (754-830)	840 (786-899)
	HI Titer ≥ 1:40 (95% CI)	97% (89%-100%)	94% (80%-99%)	100% (99%-100%)	100% (99%-100%)
	Seroconversion Rate[c] (95% CI)	97% (89%-100%)	94% (80%-99%)	43% (40%-46%)	48% (43%-52%)
B1		N = 248	N = 139	N = 765	N = 371
	GMT (95% CI)	62 (53-73)	70 (56-87)	214 (201-227)	203 (186-222)
	HI Titer ≥ 1:40 (95% CI)	76% (70%-81%)	79% (71%-86%)	99% (97%-99%)	98% (96%-99%)
	Seroconversion Rate[c] (95% CI)	76% (70%-81%)	79% (71%-86%)	63% (60%-67%)	61% (56%-66%)
B2		N = 335	N = 182	N = 674	N = 319
	GMT (95% CI)	79 (66-95)	80 (63-102)	287 (267-308)	295 (265-328)
	HI Titer ≥ 1:40 (95% CI)	76% (72%-81%)	75% (68%-81%)	99% (98%-100%)	99% (97%-100%)

Seroconversion Rate[b] (95% CI)	76% (72%-81%)	75% (68%-81%)	71% (67%-74%)	69% (64%-74%)

Sources: section 5.3.5.1, CSR V130_03 Table 14.2.1.1.4, Table 14.2.1.1.4.1, Table 14.2.1.2.4, Table 14.2.1.2.4.1, Table 14.2.1.3.4 and Table 14.2.1.3.4.1., pp.351-54

Abbreviations: HI = hemagglutination inhibition. PPS = per protocol set. GMT = geometric mean titer. CI = confidence interval. HI titer ≥ 1:40 = percentage of subjects with HI titer ≥ 1:40.

[a] Day 22 for previously vaccinated subjects, Day 50 for not previously vaccinated subjects.

[b] The comparator vaccine for A/H1N1, A/H3N2 and B1 is TIV1c, for B2 the comparator vaccine is TIV2c.

[c] Seroconversion rate = percentage of subjects with either a pre-vaccination HI titer < 1:10 and post vaccination HI titer ≥ 1:40 or with a pre-vaccination HI titer ≥ 1:10 and a minimum 4-fold increase in post vaccination HI antibody titer.

<u>Reviewer Comment:</u> Subjects who had baseline HI antibody titers ≥1:10 achieved GMT titers that were 2-3 times higher than subjects whose baseline HI antibody titers were ≤1:10. The percentage of subjects achieving post-vaccination HI anti body titers ≥1:40 were 94% or greater for each of the two A strains regardless of baseline HI titers. However, for the two B strains, 98-99% of subjects with the higher baseline titers achieved post-vaccination HI titers ≥1:40, and only 75-79% subjects with lower baseline titers achieved post-vaccination HI titers ≥1:40. In this reviewer's opinion, higher immune responses to the B strains, observed for subjects with higher baseline HI titers, might not translate to a linear increase in vaccine effectiveness.

6.1.11.5 Exploratory and Post Hoc Analyses

N.A.

6.1.12 Safety Analyses

6.1.12.1 Methods

Study V130_03 had three co-primary safety endpoints:

1. 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).
2. 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).
3. Percentages 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).

A total 2333 subjects enrolled into the study and 2332 subjects were exposed to study vaccine and were included in the safety set. Table 16 presents the data on solicited local AEs from day 1 through day 7 after any vaccination.

Table 16. Number (%) of Subjects ≥4 to <18 Years of Age with Solicited Local Adverse Events from Day 1 Through Day 7 After Any Vaccination – Solicited Safety Set

Vaccine Group	QIVc	TIV1c	TIV2c
Induration (mm)	N=1135	N=570	N=563
Any	187 (16%)	104 (18%)	78 (14%)
Severe[a]	1 (<1%)	3 (1%)	1 (<1%)
Erythema (mm)	N=1135	N=570	N=563
Any	244 (21%)	121 (21%)	108 (19%)
Severe[a]	6 (1%)	2 (<1%)	1 (<1%)
Ecchymosis (mm)	N=1135	N=570	N=562
Any	84 (7%)	48 (8%)	41 (7%)
Severe[a]	1 (<1%)	0	0
Pain	N=952	N=479	N=469
Any	562 (59%)	277 (58%)	269 (57%)

Vaccine Group	QIVc	TIV1c	TIV2c
Severe	9 (1%)	3 (1%)	5 (1%)
Tenderness	N=183	N=91	N=94
Any	100 (55%)	46 (51%)	45 (48%)
Severe	3 (2%)	1 (1%)	2 (2%)

Source: Adapted from sBLA 125408.127, CSR for V130_03, Table 14.3.1.2.2, p.125.
Solicited AEs were reported from day 1 (includes AEs reported within 30 minutes after vaccination) through day 7.
For subjects ≥4 to <6 years of age, severe induration, ecchymosis or erythema was defined as a diameter >50 mm, respectively; accordingly, for subjects ≥6 years of age, a diameter >100mm was defined as severe.

Table 17 presents the data on solicited systemic AEs from day 1 through day 7 after any vaccination.

Table 17. Number (%) of Subjects ≥4 to <18 Years of Age with Solicited Systemic Adverse Events from Day 1 Through Day 7 After Any Vaccination – Solicited Safety Set

Vaccine Group	QIVc	TIV1c	TIV2c
Chills[a]	N=1135	N=570	N=563
Any	71 (6%)	29 (5%)	20 (4%)
Severe	3 (<1%)	5 (1%)	2 (<1%)
Nausea	N=952	N=479	N=469
Any	90 (9%)	37 (8%)	34 (7%)
Severe	6 (1%)	2 (<1%)	3 (1%)
Myalgia	N=952	N=479	N=469
Any	150 (16%)	83 (17%)	66 (14%)
Severe	5 (1%)	2 (<1%)	1 (<1%)
Arthralgia	N=952	N=479	N=469
Any	55 (6%)	32 (7%)	31 (7%)
Severe	0	1 (<1%)	1 (<1%)
Headache	N=952	N=479	N=469
Any	186 (20%)	97 (20%)	77 (16%)
Severe	8 (1%)	7 (1%)	3 (1%)
Fatigue	N=952	N=479	N=469
Any	163 (17%)	80 (17%)	79 (17%)
Severe	10 (1%)	6 (1%)	1 (<1%)
Vomiting	N=1135	N=570	N=563
Any	39 (3%)	14 (2%)	14 (2%)
Severe	2 (<1%)	0	0
Diarrhea	N=1135	N=570	N=563
Any	47 (4%)	29 (5%)	23 (4%)
Severe	1 (<1%)	1 (<1%)	1 (<1%)

Vaccine Group	QIVc	TIV1c	TIV2c
Loss of appetite	N=952	N=479	N=469
Any	90 (9%)	42 (9%)	44 (9%)
Severe	1 (<1%)	1 (<1%)	1 (<1%)
Change in Eating Habits	N=183	N=91	N=94
Any	25 (14%)	7 (8%)	7 (7%)
Severe	1 (1%)	4 (4%)	0
Sleepiness	N=183	N=91	N=94
Any	39 (21%)	12 (13%)	13 (14%)
Severe	2 (1%)	3 (3%)	1 (1%)
Irritability	N=183	N=91	N=94
Any	35 (19%)	13 (14%)	14 (15%)
Severe	3 (2%)	2 (2%)	1 (1%)
Body Temperature	N=1135	N=570	N=563
≥38.0 °C	39 (3%)	20 (4%)	13 (2%)

Source: Adapted from sBLA 125408.127, CSR for V130_03, Table 14.3.1.2.2, p.142.
Solicited AEs were reported from day 1 (includes AEs reported within 30 minutes after vaccination) through day 7.
[a]Shivering was coded as chills.

Table 18 presents the data on unsolicited AEs from day 1 through 3 weeks after last vaccination, categorized by system organ classification, and considered by the investigator to be at least possibly related to vaccination.

Table 18. Number (%) of Subjects with At Least Possibly related Unsolicited Adverse Events by System Organ Classification from from Day 1 Through 3 Weeks after Last Vaccination - Unsolicited Safety Set

Vaccine Group	QIVc	TIV1c	TIV2c
	N=1149	N=579	N=570
Any AE	56 (4.9%)	34 (5.9%)	31 (5.4%)
Blood and lymphatic system disorders	1 (0.1%)	0	0
Ear and labyrinth disorders	0	2 (0.3%)	0
Gastrointestinal disorders	10 (0.9%)	4 (0.7%)	3 (0.5%)
General disorders and administration site conditions	33 (2.9%)	19 (3.3%)	18 (3.2%)
Infections and infestations	4 (0.3%)	3 (0.5%)	5 (0.9%)
Metabolism and	2 (0.2%)	0	2 (0.4%)

Vaccine Group	QIVc	TIV1c	TIV2c
nutrition disorders			
Musculoskeletal and connective tissue disorders	4 (0.3%)	1 (0.2%)	1 (0.2%)
Nervous system disorders	13 (1.1%)	3 (0.5%)	3 (0.5%)
Psychiatric disorders	0	0	1 (0.2%)
Renal and urinary disorders	0	0	1 (0.2%)
Reproductive system and breast disorders	0	1 (0.2%)	0
Respiratory, thoracic and mediastinal disorders	6 (0.5%)	6 (1.0%)	6 (1.1%)
Skin and subcutaneous tissue disorders	3 (0.3%)	2 (0.3%)	2 (0.4%)
Vascular disorders	0	2 (0.3%)	0

Source: Adapted from sBLA 125408.127, CSR for V130_03, Table 14.3.1.19.1, p.154.

Reviewer Comment: In this reviewer's opinion the rates of unsolicited AEs and the types of these events are within the range typically seen with routine childhood vaccinations and do not raise any concerns from a safety perspective. This reviewer concurs with the determination of at least possibly related made by the investigators.

Table 19 presents data on percentage of subjects with any AE; at least possibly related AE; SAEs; at least possible related SAEs; AEs leading to study withdrawal; medically attended AEs; NOCDs and deaths.

Table 19. Number (%) of Subjects ≥4 to < 18 Years of Age with Unsolicited Adverse Events After Any Vaccination - 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: Adapted from sBLA 125408.127, CSR for V130_03, Tables 14.3.1.15.1;14.3.1.19.1; 14.3.2.2; 14.3.2.3; 14.3.2.4; 14.3.2.6; 14.3.2.7; 14.3.2.1., pp.134-135.

Abbreviation: AE-adverse events, SAE-serious adverse events, NOCD-new onset of chronic diseases.
Unsolicited AEs were collected 3 weeks after the last vaccination, whereas SAEs, medically attended AEs, AEs leading to withdrawal from the study, NOCDs were collected from day 1 through study termination.

Reviewer Comment: The one AE leading to study withdrawal was prolonged injection site induration and erythema that led to withdrawal on study day 10 after vaccination and is reported to have lasted until study day 16 and was considered to be probably related to vaccine administration.

Solicited Local AEs

Subjects ≥4 to <18 years of age

Overall, the percentages of subjects in the QIVc, TIV1c and TIV2c groups who reported solicited local AEs were 66%, 65% and 60% respectively. Across the 3 groups, the most commonly reported solicited local AE was injection-site pain (59%, 58% and 57% respectively) or tenderness for subjects ≥4 to <6 years of age (55%, 51% and 48% respectively).

Most of the solicited local AEs had their onset from 6 hours to 2 days after the vaccination and were mild to moderate in severity. The only severe solicited local AE that was experienced by >1% of subjects were injection-site tenderness (2% in both QIVc and TIV2c groups).

Subjects ≥4 to <6 years of age

Across the QIVc, TIV1c and TIV2c groups, the percentages of subjects reporting solicited local AEs were 57%, 56% and 51%, respectively after the first vaccination and 53%, 44% and 36%, respectively, after the second vaccination. In all study groups, there was a trend towards decreased percentages of subjects reporting solicited local AEs after the second vaccination than after the first vaccination. After the second vaccination, the percentages of subjects who reported solicited local AEs were higher in the QIVc group than the percentages of subjects reporting these events in the TIV1c and TIV2c groups. In the QIVc, TIV1c and TIV2c groups, the most commonly reported solicited local AE was injection-site tenderness 46%, 45% and 43%, respectively, after the first vaccination and 50%, 38% and 32%, respectively, after the second vaccination.

The severe solicited local AEs that were experienced by >1% of subjects were induration (2%) in the TIV1c group after the first vaccination, and injection-site

tenderness (4%) in the TIV2c group and erythema (2%) in QIVc group after the second vaccination.

Subjects ≥6 to <9 years of age
Across the QIVc, TIV1c and TIV2c groups, the percentages of subjects reporting solicited local AEs were 64%, 67% and 62%, respectively, after the first vaccination and 50%, 57% and 57%, respectively, after the second vaccination. In all groups, there was a trend towards decreased percentages of subjects reporting solicited local AEs after the second vaccination than after the first vaccination. In the QIVc, TIV1c and TIV2c groups the most commonly reported solicited local AE was injection-site pain 54%, 57% and 58% after the first and 46%, 54% and 53% after the second vaccination respectively. Most of the solicited local AEs were mild to moderate in severity. The only severe solicited local AE that was experienced by >1% of subjects was, injection-site pain 2% in TIV2c groups after each vaccination.

Subjects ≥9 to <18 years of age
Across the QIVc, TIV1c and TIV2c groups, the percentages of subjects reporting solicited local AEs were 65%, 60%, 55% respectively. In the QIVc, TIV1c and TIV2c, the most commonly reported solicited local AE was injection-site pain 58%, 51% and 50%, respectively. Most of the solicited local AEs were mild to moderate in severity. No severe solicited local AE that was experienced by >1% were reported.

Solicited Systemic AEs

Subjects ≥4 to <18 years of age
Overall, the percentages of subjects in the QIVc, TIV1c and TIV2c who reported solicited systemic AEs were 38%, 39% and 34% respectively. Accounting for the differences in types of solicited systemic AEs collected in subjects ≥4 to <6 years of age and subjects ≥6 to <18 years of age, the most commonly reported solicited systemic AEs reported across the 3 groups were: sleepiness (21%, 13%, and 14% respectively), irritability (19%, 14%, and 15% respectively) and change in eating habits (14%, 8%, and 7% respectively) in ≥4 to <6 years age group and headache (20%,20%, and 16% respectively), fatigue (17%, 17%, and 17% respectively), and myalgia (16%, 17%, and 14% respectively) in the ≥6 to <18 years age group in QIVc, TIV1c, and TIV2c groups, respectively.

Most of the solicited systemic AEs had their onset from 6 hours to 2 days after the vaccination and were mild to moderate in severity. Severe solicited systemic AEs that were experienced by >1% of subjects were reported in subjects 4 to <6 years of age, as follows: change in eating habits (4% in TIV1c group), sleepiness (3% in TIV1c group), irritability (3% in the TIVIc group).

The body temperature of >95%of subjects was <38°C after study vaccination. In the QIVc, TIV1c and TIV2c groups, body temperature ≥38°C was reported for 3%, 4% and 2% subjects respectively. One subject from the QIVc group experienced a body temperature ≥40°C.

Subjects ≥4 to <6 years of age

Across the QIVc, TIV1c and TIV2c groups, the percentages of subjects reporting solicited systemic AEs were 28%, 20% and 18%, respectively, after the first vaccination and 31%, 23% and 19%, respectively, after the second vaccination. In all groups, there was a trend towards decreased percentages of subjects reporting solicited systemic AEs after the second vaccination than after the first vaccination. After the second vaccination, the percentages of subjects who reported solicited systemic AEs were higher in the QIVc group than the percentages of subjects reporting these events in the TIV1c and TIV2c groups.

Reviewer Comment: Increased solicited systemic AEs following administration of QIV formulations compared to TIV formulations has been seen in other seasonal influenza vaccines. The type and severity of these AEs does not, in this reviewer's opinion, constitute a safety signal.

In the QIVc, TIV1c and TIV2c groups, the most commonly reported solicited systemic AEs were sleepiness (19%, 12%, 10% after the first and 13%, 8%, 11% after the second vaccination respectively), irritability (16%, 10%, 10% after the first and 15%, 15%, 13% after the second vaccination respectively) and change in eating habits (10%, 7%, 6% after the first and 9%, 8%, 2% after the second vaccination respectively).

Subjects ≥6 to <9 years of age

Across the QIVc, TIV1c and TIV2c groups, the percentages of subjects who reported solicited systemic AEs were 31%, 36% and 35%, respectively, after the first and 22%, 27% and 23%, respectively, after the second vaccination. There was a trend toward decreased percentages of subjects reporting solicited systemic AEs after second vaccination than after the first vaccination.

In the QIVc, TIV1c and TIV2c groups, the most commonly reported solicited systemic AEs were headache (14%, 13%, 12% after the first and 4%, 7%, 6% after the second vaccination respectively), fatigue (13%, 14% 18% after the first and 9%, 11%, 9% after the second vaccination respectively) and myalgia (12%, 14%, 10% after the first and 9%,10%, 9% after the second vaccination respectively).

Most of the solicited systemic AEs were mild to moderate in severity. Severe solicited systemic AEs that were experienced by >1% of subjects were fatigue 2% in the QIVc group after the first vaccination and 2% in TIV1c group after the second vaccination.

Subjects ≥9 to <18 years of age

Across the QIVc, TIV1c and TIV2c groups, the percentages of subjects reporting solicited systemic AEs were 40%, 41%, 33% respectively. In the QIVc, TIV1c and TIV2c groups, the most commonly reported solicited systemic AEs were headache (22%, 23%, 18% respectively), fatigue (18%, 16%, 16% respectively) and myalgia (16%, 17%, 15% respectively).

Most of the solicited systemic AEs were mild to moderate in severity, and severe solicited systemic AEs that were experienced by >1% of subjects were headache (2% in the TIV1c group).

Unsolicited AEs

The percentages of subjects reported unsolicited AEs in the QIVc, TIV1c and TIV2c groups were comparable (24.3%, 24.0% and 26.7% respectively). Across the groups, the most commonly reported categories of unsolicited AEs were classified under the medical dictionary for regulatory activities (MedDRA) system organ class (SOCs) of 'infections and infestations' (7.3%, 7.3% and 10.4% respectively), 'respiratory, thoracic and mediastinal disorders'(6.9%, 8.3% and 7.4% respectively) 'general disorders and administrative site conditions'(5.5%, 5.9% and 6.7% respectively).

Unsolicited AEs assessed by the investigator as at least possibly related to the study vaccine were comparable across the QIVc, TIV1c and TIV2c groups (4.9%, 5.9% and 5.4% respectively). The percentages of AEs judged by the investigator as possibly related to the study vaccine were most frequent in the SOC 'General Disorders and Administrative Site Conditions' (2.9%, 3.3% and 3.2% respectively).

Similar trends for unsolicited AEs were observed in subjects ≥4 to <9 years of age and ≥9 to <18 years of age.

6.1.12.3 Deaths

There were no deaths reported during the study.

6.1.12.4 Nonfatal Serious Adverse Events

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 as related to the study vaccines.

Reviewer Comment: *This reviewer concurs with the investigator determination that they are not likely to be related to the administration of the study vaccine.*

Table 20 presents that data related to SAEs.

Table 20. All SAEs by Subject Number, Treatment Group, MedDRA Term and Relationship to Vaccine

Subject Number/group	MedDRA term	Relationship to vaccine
1. 1223010 / QIVc	Depression	none
2. 1293017 / QIVc	Bipolar disorder	none
3. 1593022 QIVc	Mild Traumatic Brain Injury	none
4. 1343010/ QIVc	Partial seizures	none
5. 1671028 /QIVc	Anaphylactic reaction [to Bactrim, not to study vaccine]	none
6. 2033001 /QIVc	Oppositional defiant disorder	none
7. 1341023/TIV1c	Forearm fracture	none
8. 1363006 /TIV1c	Suicidal ideation	none
9. 1481021 /TIV1c	Periorbital cellulitis	none
10. 1701011/ TIV1c	HSP [HENOCH SCHONLEIN PURPURA]	none
11. 1903002/ TIV1c	Suicide attempt	none
12. 1903016/ TIV1c	Appendicitis	none
13. 1913027 /TIV1c	Major depression	none
14. 1562016 /TIV2c	Sleep apnea syndrome	none
15. 1731002/ TIV2c	Gastroenteritis	none

Source: Adapted from sBLA 125408.127, CSR for V130_03, Table 14.3.2.9, p.2450.

6.1.12.5 Adverse Events of Special Interest (AESI)

N.A.

6.1.12.6 Clinical Test Results

N.A.

6.1.13 Study Summary and Conclusions

Study V130_03 met both of the co-primary immunogenicity endpoints and all three of the secondary immunogenicity endpoints and the safety data did not reveal a safety signal. However, these data do not support the safety and immunogenicity of Flucelvax QIVc for the pediatric age group by a traditional pathway because the comparator vaccine, Flucelvax Trivalent, is not, at the time of this review, a U.S. licensed trivalent influenza vaccine. The data do support an AA pathway based upon CBER immunogenicity criteria for a seasonal influenza vaccine. [Please see Section I, Executive Summary; Section 10, Conclusions; and Section 11.4, Recommendations for Regulatory Action for details and discussion of the accelerated approval pathway for this age group of >4 years to <18 years].

6.2 Trial #2

Study: V130_01: A Phase III, Stratified, Randomized, Double-Blind, Multicenter, Non-Inferiority Study to Evaluate the Safety and Immunogenicity of a Cell-based Quadrivalent Subunit Influenza Virus Vaccine and Cell-based Trivalent Subunit Influenza Virus Vaccines in Adults Ages ≥18 Years of Age

6.2.1 Objectives (Primary, Secondary)

Study V130_01 was designed to assess the immunogenicity and the safety of the quadrivalent formulation of Flucelvax, QIVc, compared to the trivalent formulation of Flucelvax, TIVc, on the co-primary immunogenicity endpoints of non-inferiority of antibody responses of QIVc to 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 4 vaccine strains; and non-inferiority of antibody responses of QIVc to comparator TIV1c 3 weeks after vaccination (day 22) in adults ≥18 years of age, as assessed by differences in seroconversion rates for each of the 4 vaccine strains separately after vaccination.

6.2.2 Design Overview

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

Reviewer Comment: The study design is appropriate to generate definitive data to support the desired indication; is the same study design used by other influenza vaccine manufacturers for their quadrivalent formulations and was approved by CBER in consultations before the beginning of this Phase III study.

This design allows for the determination of the immunogenicity of the second B strain and for the determination that the addition of this second B strain does not interfere with the immune responses to the other three strains in the quadrivalent formulation.

6.2.3 Population

The study enrolled 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 vaccination

The exclusion criteria were the same as for study V130_03.

There were 40 U.S. sites.

6.2.4 Study Treatments or Agents Mandated by the Protocol

The study vaccines (QIVc, TIV1c, TIV2c) are the same as used in study V130_03.

6.2.5 Directions for Use

The directions for use are the same as for study V130_03.6.2.6 Sites and Centers

6.2.7 Surveillance/Monitoring

Schedule of Events:

Table 21. Time and Events Table

Visit Type	Treatment Period				Follow-up Period		Unscheduled Study
	Clinic Visit	Reminder Call	Reminder Call	Clinic Visit	Safety Telephon	Clinic Visit	Clinic Visit
Visit Number	1	--	--	2	3[d], 4, 5,	8	--
Study Day	1	3	5	22	30[d], 60, 90, 120,	181	--
Study Visit Time Window	Not applicabl	2-4 days postvaccinatio	4-6 days postvaccinatio	20-29 days post	-7/+7 days	165-195 days post	Day 1 through181
Informed	X[b]						
Exclusion/Inclusi	X[b]						
Medical history	X[b]						
Review of	X[b]			X		X	X
Physical	X[b]						
Brief history/Symptom				X		X	X
Pregnancy test (only for females of childbearing	X[b]			X		X	
Blood draw	X[b]			X			
Study vaccine	X						
30 minutes post injection assessment	X						
Diary card	X						
Diary card		X	X				
Diary card				X			
Scripted safety					X		
Assess all AEs[k]	X			X			X[j]
Assess SAEs[l]	X			X	X	X	X[j]
Assess Medically Attended AEs	X			X	X	X	X[j]
Assess	X			X			X[j]
Concomitant	X			X	X	X	X[j]
Study						X	

Source: Adapted from sBLA 125408.127, CSR for V130_01,Table 4 Protocol version 2, dated 06 May 14.
Abbreviations: AE-adverse events; NOCDs-new onset chronic diseases; SAE-serious adverse event, min-minimum, max-maximum.

[a] An unscheduled study visit could be performed under the following circumstances: further evaluation of safety information that is described on the telephone that is to be investigated further at any time during the study or evaluation of influenza-like symptoms (only from day 1 through day 22).
[b] Procedure that was to be performed prior to vaccination.
[c] While there could be a possibility of overlap in the visit windows for the reminder calls (i.e., 4 days post vaccination), each reminder call was to be made on 2 separate days; both reminder calls were not to be made on the same day.

6.2.8 Endpoints and Criteria for Study Success

There were two co-primary immunogenicity endpoints:

1. The ratio of geometric mean titer (GMT) at 3 weeks after vaccination (day 22) for each of the 4 vaccine strains. Criteria for success was the upper bound of the 2-sided 95% CI for the ratio of GMTs (GMTTIV1c or TIV2c /GMTQIVc) for HI antibody should not exceed the non-inferiority margin of 1.5
2. The differences in seroconversion rates for each of the 4 vaccine strains separately after vaccination. Criteria for success was 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 non-inferiority objectives were achieved.

There were three secondary immunogenicity endpoints:

1. The antibody responses to all 4 influenza vaccine strains after vaccination in the age cohorts:18 to ≤65 years and 65 years and older according to the Committee for Medicinal Products for Human Use (CHMP)..
2. The superiority of antibody responses to the first B strain (B1) in QIVc as compared to TIV2c (containing the B2 strain) as assessed by GMT ratios and seroconversion rates in adults ≥18 years of age. Criteria for success was the upper bound of the 2-sided 95% CI for the ratio of GMTs (GMT TIV1c or TIV2c /GMTQIVc) for HI antibody should not exceed the superiority margin of 1.0; the lower bound of the 2-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody should meet or exceed 40%. The lower bound of the 2-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥1:40 should meet or exceed 70%.
3. The superiority of antibody responses to the second B strain (B2) in QIVc as compared to TIV1c (containing the B1 strain) as assessed by GMT ratios and seroconversion2 rates in adults ≥18 years of age. Criteria for success was the upper bound of the 2-sided 95% CI for the ratio of GMTs (GMT TIV1c or TIV2c /GMTQIVc) for HI antibody should not exceed the superiority margin of 1; the lower bound of the 2-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody should meet or exceed 40%. The lower bound of

the 2-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥1:40 should meet or exceed 70%.

There was one primary safety endpoint:
1. The safety and tolerability of QIVc, TIV1c, and TIV2c in adults ≥18 years of age.

The statistical assessment of each of the endpoints was pre-specified in the SAP of the study and is referenced below [in section 6.2.11.1 and section 6.2.11.2] in each table that presents the immunogenicity results of the study. There were no changes made to the study endpoints during the study.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Please refer to the statistical review for details concerning the Statistical Analysis Plan [SAP].

The primary population analyzed for the non-inferiority assessment was the per protocol set (PPS). CBER criteria for immunogenicity and superiority were assessed using the full analysis set (FAS), which consisted of all subjects in the enrolled population who received the study vaccination and provided immunogenicity data at the day(s) of baseline (prior to first vaccination) and 3 weeks after the (last) vaccination. The FAS populations were analyzed “as randomized”, i.e., according to the vaccine a subject was designated to receive, which could have been different from the vaccine actually received. The PPS included all subjects in FAS that correctly received the study vaccine(s), had no major protocol deviations leading to exclusion, and were not excluded due to other reasons (e.g., withdrawal of consent, influenza-like illness). All populations were considered by objective and/or time point, meaning sometimes not all data of a subject but only part of it was removed from the PPS analysis.

No changes were made to the SAP.

6.2.10 Study Population and Disposition

See Section 6.2.10

6.2.10.1 Populations Enrolled/Analyzed

Table 22 presents the numbers of subjects who were enrolled, completed the study per protocol, were withdrawn and were lost to follow-up.

Table 22. Summary of Study Termination – All Enrolled Set

	Number (%) of subjects		
Vaccine Group	**QIVc**	TIV1c	TIV2c
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%)

Source: Adapted from sBLA 125408.127, CSR for V130_01, Table 14.1.1.2, p.237.
AE:adverse events.

Reviewer Comment: 96% of all subjects in each treatment group completed the study per protocol and the proportion of subjects who were withdrawn or who were lost to follow-up is balanced between the groups. In this reviewer's opinion the percentage of withdrawn or lost to follow-up is not clinically significant.

6.2.10.1.1 Demographics
See section 6.2.10.1.2, Table 23

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 23 presents the demographic and baseline characteristics of the enrolled population.

Table 23. Demographic and Baseline Characteristics - All Enrolled Set

	Number (%) of subjects		
	QIVc	**TIV1c**	**TIV2c**
	N=1335	N=676	N=669
Age (years)±SD	57.4±17.82	57.2±17.98	57.1±18.09
Sex			
Male	603 (45.2%)	284 (42.0%)	277 (41.4%)
Female	732 (54.8%)	392 (58.0%)	392 (58.6%)
Height (cm) ±SD	169.36±9.884	168.78±10.299	168.62±10.123
Weight (kg) ±SD	86.90±22.726	86.20±21.306	85.79±22.132
Body Mass Index (kg/m^2)±SD	30.22±7.257	30.19±6.740	30.16±7.358
Race/Ethnicity			

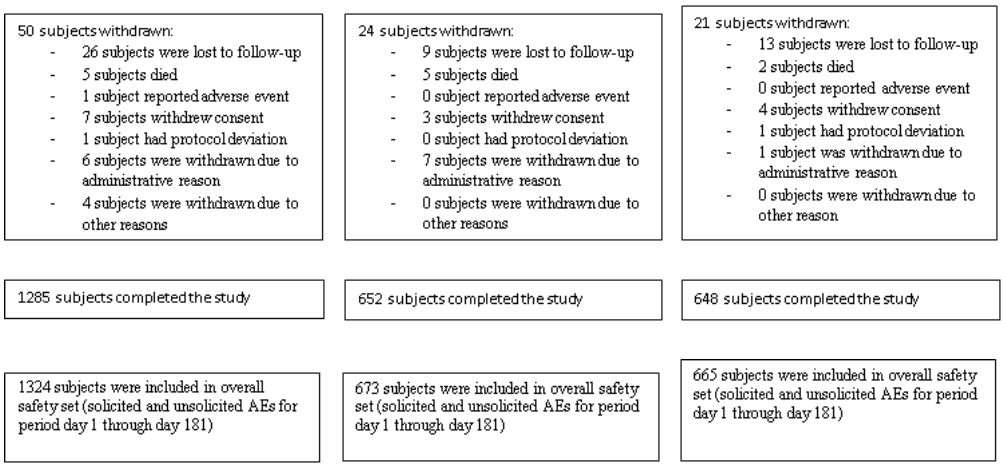
	Number (%) of subjects		
	QIVc	**TIV1c**	**TIV2c**
	N=1335	N=676	N=669
Asian	4 (0.3%)	3 (0.4%)	3 (0.4%)
American Indian	10 (0.7%)	7 (1.0%)	2 (0.3%)
Black	179 (13.4%)	80 (11.8%)	81 (12.1%)
Native Hawaiian	2 (0.1%)	2 (0.3%)	0 (0.0%)
Hispanic	122 (9.1%)	59 (8.7%)	53 (7.9%)
Caucasians	1009 (75.6%)	519 (76.8%)	525 (78.5%)
Other	9 (0.7%)	6 (0.9%)	5 (0.7%)
Met entry criteria			
yes	1334 (99.9%)	676 (100%)	669 (100%)
Previous influenza vaccination			
yes	326 (24.4%)	172 (25.4%)	168 (25.1%)
Female of child bearing potential			
Yes	171 (12.8%)[a]	101 (14.9%)[a]	107 (16.0%)[a]
No	561 (42.0%)[a]	291 (43.0%)[a]	285 (42.6%)[a]
Pregnancy test			
Positive	0 (0.0%)	0 (0.0%)	0 (0.0%)
Negative	199 (14.9%)[a]	111 (16.4%)[a]	123 (18.4%)[a]
Not Done	533 (39.9%)	281 (41.6%)[a]	269 (40.2%)[a]

Source: Adapted from sBLA 125408.127, CSR for V130_01,Table 14.1.1.3, p.240
[a] the percentages are based upon enrolled population.

Reviewer Comment: There were more females than males in the study by about 10%. The racial/ethnic composition of the study subjects generally reflects that in the U.S. The proportion of subjects with previous influenza vaccination is balanced between the three groups. In this reviewer's opinion the study sufficiently reflects the U.S. population and the results should be able to be extrapolated to that population.

6.2.10.1.3 Subject Disposition

Figure 2. Subject Disposition Flowchart



Source: Adapted from sBLA 125408.127, CSR for V130_01Table 14.1.1.2; Table 14.1.1.2.1; Table 14.1.1.1.2.; pp.106.

6.2.11 Efficacy Analyses

The results for the two co-primary endpoints are presented in subsection 6.2.11.1. The results for the secondary endpoints are presented in subsection 6.2.11.2.

6.2.11.1 Analyses of Primary Endpoint(s)

The first co-primary endpoint for Study V130_1 was the demonstration of non-inferiority of antibody responses of QIVC to comparator TIV1c based upon the ratio of GMT for each of the 4 vaccine strains, separately, after vaccination. These results are presented in Table 24. The second co-primary endpoint was the demonstration of the non-inferiority of QIVc compared to TIVc as determined by seroconversion rates for each of the 4 vaccine strains and these results are presented in Table 25.

Table 24. Geometric Mean Titers (95% CI), and Vaccine Group Ratios, 3 Weeks After the Vaccination, HI Assay-Per Protocol Set

	QIVc	**TIV1c/or/TIV2c[a]**	**Vaccine Group Ratio**
H1N1	N=1250	N=635	
Day 22	302.8	298.9	1.0
	(281.8-325.5)	(270.3-330.5)	(0.9-**1.1**)
H3N2	N=1250	N=635	
Day 22	372.3	378.4	1.0
	(349.2-396.9)	(345.1-414.8)	(0.9-**1.1**)

B1 Day 22	N=1250 133.2 (125.3-141.7)	N=635 115.6 (106.4-125.6)	 0.9 (0.8-**1.0**)
B2 Day 22	N=1250 177.2 (167.6-187.5)	N=639 164.0 (151.4-177.7)	 0.9 (0.9-**1.0**)

Source: Adapted from sBLA 125408.127, CSR for V130_01, Table 14.2.1.3, p.521
Abbreviation: CI-confidence interval, HI- hemagglutination inhibition
[a]For H1N1, H3N2 and B1 strain ratio of GMTs was calculated as TIV1c/QIVc, whereas for B2 strain ratio of GMTs was calculated as TIV2c/QIVc.
Result: Met non-inferiority criteria; The upper bound of the 2-sided 95% CI for the ratio of GMTs (GMT_{TIV1}c or $_{TIV2c}$ /GMT_{QIVc}) for HI antibody should not exceed the non-inferiority margin of 1.5.

Table 25. Number (%) of Subjects with Seroconversion (95% CI) and Vaccine Group Differences, 3 Weeks After the Vaccination, HI Assay – Per Protocol Set

	QIVc	**TIV1c/or/TIV2c[a]**	**Vaccine Group Difference**
H1N1 Day 22	N=1250 615 (49.2%) (46.4%-52.0%)	N=635 309 (48.7%) (44.7%-52.6%)	 -0.5% (-5.3%-**4.2**%)
H3N2 Day 22	N=1250 479 (38.3%) (35.6%-41.1%)	N=635 226 (35.6%) (31.9%-39.5%)	 -2.7% (-7.2%-**1.9**%)
B1 Day 22	N=1250 457 (36.6%) (33.9%-39.3%)	N=635 221 (34.8%) (31.1%-38.7%)	 -1.8% (-6.2%-**2.8**%)
B2 Day 22	N=1250 497 (39.8%) (37.0%-42.5%)	N=639 226 (35.4%) (31.7%-39.2%)	 -4.4% (-8.9%-**0.2**%)

Source: Adapted from sBLA 125408.127, CSR for V130_01, Table 14.2.1.2., p.435
Abbreviation: CI-confidence interval, HI- hemagglutination inhibition
[a]For H1N1, H3N2 and B1 strain differences in seroconversion was calculated as TIV1c/QIVc, whereas for B2 strain differences in seroconversion was calculated as TIV2c/QIVc.
Results: Met non-inferiority criteria; 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%.

*<u>Reviewer Comment</u>**:** Study V130_01 demonstrated the non-inferiority of the quadrivalent formulation of Flucelvax compared to the trivalent formulation for each antigen by both ratios of GMT and by percentage seroconversion, each shown three weeks post vaccination. These results show that the quadrivalent formulation does not interfere with the immune responses to the two A strains*

and the first B strain and in addition provide immune responses to the second B strain. Depending upon the circulating strains in any particular year, there may be additional clinical protection from acute influenza infection afforded by the second B strain immune responses.

6.2.11.2 Analyses of Secondary Endpoints

The first of the secondary immunogenicity endpoints for Study V130_01 was to demonstrate per CBER criteria that both the QIVc and TIVc formulations met seroconversion criteria and the criteria for the percentage of subjects achieving HI titers ≥1:40, 3 weeks after vaccination. Table 26 presents the data for seroconversion and Table 27 present the data for HI Titer ≥1:40.

Table 26. Number (%) of Subjects ≥18 to <65 Years and ≥65 Years of Age with Seroconversion (95% CI), 3 Weeks After the Vaccination HI Assay- Full Analysis Set

	≥18 to <65 Years		**≥65 Years**	
	QIVc	**TIV1c/or/TIV2c[a]**	**QIVc**	**TIV1c/or/TIV2c[a]**
H1N1 Day 22	N=661 417 (63.1%) (**59.3**%-66.8%)	N=328 198 (60.4%) (**54.8**%-65.7%)	N=650 224 (34.5%) (**30.8**%-38.3%)	N=336 124 (36.9%) (**31.7%**-42.3%)
H3N2 Day 22	N=661 325 (49.2%) (**45.3**%-53.1%)	N=328 155 (47.3%) (**41.7**%-52.8%)	N=650 177 (27.2%) (**23.8%-**30.8%) **[CBER criteria not met]**	N=336 83 (24.7%) (**20.2%-**29.7%)
B1 Day 22	N=661 344 (52.0%) (**48.2**%-55.9%)	N=328 165 (50.3%) (**44.8**%-55.8%)	N=650 136 (20.9%) (**17.9%-**24.3%) **[CBER criteria not met]**	N=336 65 (19.3%) (15.3%-24.0%)
B2 Day 22	N=661 349 (52.8%) (**48.9**%-56.7%)	N=326 164 (50.3%) (**44.7**%-55.9%)	N=650 171 (26.3%) (**23.0%-**29.9%) **[CBER criteria not met]**	N=332 69 (20.8%) (16.5%-25.6%)

Source: Adapted from sBLA 125408.127, CSR for V130_01, Table 14.2.1.6.4, p.740.
Abbreviation: CI-confidence interval, HI- hemagglutination inhibition
[a] For H1N1, H3N2 and B1 strain TIV1c data is presented , whereas for B2 strain TIV2c data is presented.

Results: CBER immunogenicity criteria met for age cohort ≥18 to <65 Years: The lower bound of the 2-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody met or exceed 40%. For ≥65 years, however The lower bound of the 2-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody should did not meet or exceed 30%,for either the QIVC or the TIV1c or TIV2c groups for H3N2 or B1 or B2 strains.

Table 27. Number (%) of Subjects ≥18 to <65 Years and .≥65 Years of Age with HI Titer ≥1:40 (95% CI), 3 Weeks After the Vaccination, HI Assay- Full Analysis Set

	≥18 to <65 Years		**≥65 Years**	
	QIVc	**TIV1c/or/TIV2c[a]**	**QIVc**	**TIV1c/or/TIV2c[a]**
H1N1 Day 22	N=661 651 (98.5%) (**97.2**%-99.3%)	N=328 318 (97.0%) (**94.5**%-98.5%)	N=650 613 (94.3%) (**92.2**%-96.0%)	N=336 323 (96.1%) (**93.5**%-97.9%)
H3N2 Day 22	N=661 652 (98.6%) (**97.4**%-99.4%)	N=328 325 (99.1%) (**97.4**%-99.8%)	N=650 639 (98.3%) (**97.0**%-99.2%)	N=336 330 (98.2%) (**96.2**%-99.3%)
B1 Day 22	N=661 632 (95.6%) (**93.8**%-97.0%)	N=328 314 (95.7%) (**92.9**%-97.6%)	N=650 599 (92.2%) (**89.8**%-94.1%)	N=336 295 (87.8%) (**83.8**%-91.1%)
B2 Day 22	N=661 655 (99.1%) (**98.0**%-99.7%)	N=326 322 (98.8%) (**96.9**%-99.7%)	N=650 625 (96.2%) (**94.4**%-97.5%)	N=332 316 (95.2%) (**92.3**%-97.2%)

Source: Adapted from sBLA 125408.127, CSR for V130_01, Table 14.2.1.5.4, p.656.
Abbreviation: CI-confidence interval, HI- hemagglutination inhibition
[a]For H1N1, H3N2 and B1 strain TIV1c data is presented , whereas for B2 strain TIV2c data is presented.

Results**:** CBER immunogenicity criteria met within this age cohort. For ≥18 to <65 years; The lower bound of the 2-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥1:40 met or exceed 70%. For ≥65 years; The lower bound of the 2-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥1:40 met or exceed 60%.

Reviewer comment: The data show that subjects 18 years to <65 years who received QIVC vaccine achieved seroconversion by CBER criteria and >93% achieved HI antibody titer ≥1:40 three weeks after vaccination. Subjects ≥65

years who received QIVC vaccine achieved seroconversion only for the H1N1 strain, however >89% achieved HI antibody titer ≥1:40 three weeks after vaccination. In this reviewer's opinion these findings of failure to achieve seroconversion in older subjects for three strains is not unusual due to subject age, is consistent for both the QIVC and the TIVC formulations and is not likely to be clinically significant.

The second of the secondary objectives for Study V130_01 was to to demonstrate superiority of antibody responses to the first influenza B strain (B1) in QIVc as compared to TIV2c (containing the alternative influenza B (B2) strain) and the second B influenza strain (B2) in QIVc as compared to TIV1c (containing the B1 influenza strain) as assessed by GMT ratios and sero-conversion rates in subjects ≥4 to <18 years of age. Tables 28-31 present that data.

Table 28. Geometric Mean Titers (95% CI) and Vaccine Group Ratio for B1 Strain, 3 Weeks After the Vaccination, HI Assay - Full Analysis Set

	QIVc	**TIV2c**	**Vaccine Group Ratio**
	N=1311	N=657	
Day 22	177.1 (167.8-187.1)	76.3 (70.4-82.7)	0.5 (0.5-**0.5)**

Source: Adapted from sBLA 125408.127, CSR for V130_01,Table 14.2.1.7.8, p.862.
Abbreviation: CI-confidence interval, HI- hemagglutination inhibition

Results: Met superiority criteria: 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 superiority margin of 1.

Table 29. Number (%) of Subjects with Seroconversion (95%CI) and Vaccine Group Difference for B1 Strain, 3 Weeks After the Vaccination, HI Assay - Full Analysis Set

	QIVc	**TIV2c**	**Vaccine Group Difference**
	N=1311	N=657	
Day 22	39.7% (37.0%-42.4%)	18.0% (15.1%-21.1%)	-21.7% (-25.5%, **-17.7%)**

Source: Adapted from sBLA 125408.127, CSR for V130_01,Table 14.2.1.6.8, p.776.
Abbreviation: CI-confidence interval, HI- hemagglutination inhibition

Results: Superiority criteria met: The upper bound of the 2-sided 95% CI for the difference between seroconversion rates (% TIV1c or TIV2c – %seroconversion QIVc) for HI antibody should not exceed the margin of 10%.

Table 30. Geometric Mean Titers (95% CI) and Vaccine Group Ratio for B2 Strain, 3 Weeks After the Vaccination, HI Assay - Full Analysis Set

	QIVc	TIV1c	Vaccine Group Ratios
	N=1311	N=664	
Day 22	135.4 (127.6-143.7)	91.7 (85.7-98.2)	0.6 (0.6-**0.7)**

Source: Adapted from sBLA 125408.127, CSR for V130_01 Table 14.2.1.7.9. p.863.
Abbreviation: CI-confidence interval, HI- hemagglutination inhibition
Results: Met superiority criteria: 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 superiority margin of 1.0.

Table 31. Number (%) of Subjects with Seroconversion (95%CI) and Vaccine Group Difference for B2 Strain. 3 Weeks After the Vaccination, HI Assay - Full Analysis Set

	QIVc	TIV1c	Vaccine Group Difference
	N=1311	N=664	
Day 22	36.6% (34.0%-39.3%)	17.2% (14.4%-20.3%)	-19.4% (-23.2%, **-15.5%)**

Source: Adapted from sBLA 125408.127, CSR for V130_01, Table 14.2.1.6.9, p.777
Abbreviation: CI-confidence interval, HI- hemagglutination inhibition
Results: Superiority criteria met: 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 0.

Reviewer Comment: The secondary immunogenicity endpoints were met and demonstrate that the CBER criteria for percentage of subjects showing seroconversion and the percentage of subjects showing HI titers ≥1:40 were met for both the QIVc and TIVc formulations; and that superiority of antibody responses to the first influenza B strain (B1) in QIVc as compared to TIV2c (containing the alternative influenza B (B2) strain) and the second B influenza strain (B2) in QIVc as compared to TIV1c (containing the B1 influenza strain) as assessed by GMT ratios and sero-conversion rates, were met. Meeting these secondary endpoints as well as meeting the two co-primary endpoints provides support for the requested indication of active immunization against influenza for the strains contained in the annual vaccine and support that the addition of the second B strain should not interfere with immune responses to the first B strain or to the two A strains.

6.2.11.3 Subpopulation Analyses

In this sub-section differences in immunogenicity results that may vary by age, sex, race/ethnicity and baseline HI titers are presented and discussed.

Age Differences:

Immunogenicity results in influenza vaccines may vary by age, sex and HI antibody titer at baseline. Table 32 shows the GMT titters and seroconversion rates for all strains by two age cohorts, 18 to <65 years and >65 years.

Table 32. Immunogenicity Results at 3 Weeks After Vaccination in Subjects 18 Years of Age and Above, by Age, HI Assay – PPS

		18 to < 65 Years of Age				65 Years of Age and Above			
	Day 22	**QIVc N = 629**	**TIV1c/or/ TIV2c[a] N = 309/N = 316**	**Vaccine Group Ratio[b] (95% CI)**	**Vaccine Group Difference[c] (95% CI)**	**QIVc N = 1250**	**TIV1c/or/ TIV2c[a] N = 635/N = 639**	**Vaccine Group Ratio[b] (95% CI)**	**Vaccine Group Difference[c] (95% CI)**
A/H1N1	GMT (95% CI)	472.2 (429.4, 519.2)	432.2 (374.7, 498.5)	0..9 (0.8, **1.1**)	NA	193.1 (175.3, 212.8)	210.7 (184.8, 240.2)	1.1 (0.9, **1.2**)	NA
	Seroconversion Rate[d] (95% CI)	**63.3%** (59.4, 67.1)	60.2% (54.5, 65.7)	NA	-3.1% (-9.7, **3.4**)	34.9% (31.2, 38.8)	37.7% (32.4, 43.2)	NA	2.8% (-3.5, **9.2**)
A/H3N2	GMT (95% CI)	414.1 (379.4, 452.0)	410.5 (361.5, 466.0)	1.0 (0.9, **1.1**)	NA	334.2 (304.5, 366.9)	350.3 (306.7, 400.0)	1.0 (0.9, **1.1**)	NA
	Seroconversion Rate[d] (95% CI)	49.1% (45.2, 53.1)	46.6% (40.9, 52.3)	NA	-2.5 (-9.2, **4.2**)	27.4% (20.5, 30.2)	25.2% (20.5, 30.2)	NA	-2.2% (-7.9, **3.7**)
B1	GMT (95% CI)	186.6 (171.0, 203.5)	167.7 (149.5, 188.1)	0.9 (0.8, **1.0**)	NA	94.7 (87.5, 102.4)	81.3 (73.1, 90.4)	0.9 (0.8, **1.0**)	NA
	Seroconversion Rate[d] (95% CI)	52.0% (48.0, 56.0)	50.5% (44.8, 56.2)	NA	-1.5% (-8.2, **5.2**)	20.9% (17.8, 24.3)	19.9% (15.7, 24.7)	NA	-1.0% (-6.2, **4.5**)
B2	GMT (95% CI)	225.9 (208.9, 244.3)	198.4 (176.9, 222.5)	0.9 (0.8, **1.0**)	NA	138.6 (128.5, 149.5)	136.2 (122.2, 151.9)	1.0 (0.9, **1.1**)	NA
	Seroconversion	52.5%	50.3%	NA	-2.2%	26.9%	20.7%	NA	-6.2%

version Rated (95% CI)	(48.5, 56.4)	(44.7, 56.0)	(-8.8, **4.5**)	(23.4, 30.6)	(16.5, 25.6)	(-11.6, **-0.4**)

Sources: section 5.3.5.1, CSR V130_01 Table 14.2.1.2.4 and Table 14.2.1.3.4..pp.483 and 569.
Abbreviations: HI = hemagglutination inhibition. PPS = per protocol set. GMT = geometric mean titer. CI = confidence interval.
[a] The comparator vaccine for non-inferiority comparisons for A/H1N1, A/H3N2 and B1 is TIV1c, for B2 it is TIV2c. [b] $GMT_{TIV1c/TIV2c}/GMT_{QIVc}$.
[c] Seroconversion rate TIV1c/TIV2c – seroconversion rate QIVc. [d] Seroconversion rate = percentage of subjects with either a pre-vaccination HI titer < 1:10 and post vaccination HI titer ≥ 1:40 or with a pre-vaccination HI titer ≥ 1:10 and a minimum 4-fold increase in post vaccination HI antibody titer.
Bold = Non-inferiority criterion met. Please note that study V130_01 was not formally powered to assess non-inferiority in the subgroups presented in this table.

<u>Reviewer Comment</u>: The GMT titers obtained at three weeks post-vaccination are consistently higher in the age group 18 to<65years compared to the age group >65 years and this is a finding that is consistent with numerous previous studies of various influenza vaccines and is probably clinically significant in that influenza infection rates are generally higher in this older age group. The ratio of the GMT titers of QIVc to TIVc are similar, however, within each age group, indicating that these two different formulations give similar GMT titer results per age group even though the titers are significantly higher for the younger age group . A similar pattern is seen with the seroconversion rates which are significantly and consistently higher in the younger age group but which are similar between the QIVc and TIVc formulations within each age group. In this reviewer's opinion it is likely that the lower immune response by age of the subject is clinically significant and may be the reason influenza infection rates are higher in those >65 years whether or not they have received an annual influenza vaccine.

Sex differences:
Table 3.3.2-1 in the Integrated Summary of Efficacy [ISE], p.47 [not shown] evaluated the differences by sex in the immune responses as measured by GMT titers, percentage of subjects with HI antibody titers ≥1:40 and seroconvesion rates. There is no significant difference by sex for any of these three parameters for any of the four strains.

Race/ethnicity differences:
Table 33 presents the immune response data by race/ethnicity for subjects 18 years and older

Table 33. Immunogenicity Results of Subjects 18 Years of Age and Above, by Race/Ethnicity, HI Assay – PPS

		Black		Caucasian		Hispanic	
	Day 22	QIVc N = 163	TIV1c/or/ TIV2c[a] N = 73/N = 73	QIVc N = 951	TIV1c/or/ TIV2c[a] N = 491/ N = 506	QIVc N = 113	TIV1c/or/ TIV2c[a] N = 54/N = 50
A/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)
	HI Titer ≥ 1:40 (95% CI)	98.2% (94.7%-99.6%)	95.9% (88.5%-99.1%)	95.8% (94.3%-97.0%)	96.3% (94.3%-97.8%)	98.2% (93.8%-99.8%)	100.0% (93.4%-100.0%)
	Seroconversion Rate[b] (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%)
A/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)
	HI Titer ≥ 1:40 (95% CI)	98.8% (95.6%-99.9%)	98.6% (92.6%-100.0%)	98.5% (97.5%-99.2%)	98.8% (97.4%-99.6%)	96.5% (91.2%-99.0%)	98.1% (90.1%-100.0%)
	Seroconversion Rate[b] (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%)
B2	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)
	HI Titer ≥ 1:40 (95% CI)	97.5% (93.8%-99.3%)	98.6% (92.6%-100.0%)	92.4% (90.6%-94.0%)	90.4% (87.5%-92.9%)	96.5% (91.2%-99.0%)	92.6% (82.1%-97.9%)
	Seroconversion Rate[b] (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%)

		Black		Caucasian		Hispanic	
	Day 22	QIVc N = 163	TIV1c/or/ TIV2c[a] N = 73/N = 73	QIVc N = 951	TIV1c/or/ TIV2c[a] N = 491/ N = 506	QIVc N = 113	TIV1c/or/ TIV2c[a] N = 54/N = 50
B1	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)
	HI Titer ≥ 1:40 (95% CI)	100% (97.8%-100.0%)	97.3% (90.5%-99.7%)	97.2% (95.9%-98.1%)	96.6% (94.7%-98.0%)	98.2% (93.8%-99.8%)	98.0% (89.4%-99.9%)
	Seroconversion Rate[b] (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%)

Sources: section 5.3.5.1, CSR V130_01 Table 14.2.1.1.2, Table 14.2.1.2.2 and Table 14.2.1.3.2., pp. 449-452.
Abbreviations: HI = hemagglutination inhibition. PPS = per protocol set. GMT = geometric mean titer. CI = confidence interval. HI titer ≥ 1:40 = percentage of subjects with HI titer ≥ 1:40.
[a] The comparator vaccine for A/H1N1, A/H3N2 and B1 is TIV1c, for B2 the comparator vaccine is TIV2c.
[b] Seroconversion rate = percentage of subjects with either a pre-vaccination HI titer < 1:10 and post vaccination HI titer ≥ 1:40 or with a pre-vaccination HI titer ≥ 1:10 and a minimum 4-fold increase in post vaccination HI antibody titer.

Reviewer Comment: There is a pattern evident in this data that shows that in general blacks have better immune responses than Hispanics and whites have the lowest immune responses of the three groups. This pattern is evident for GMT titers and for seroconversion rates but is not evident for percentage of subjects achieving HI titers≥1:40. This pattern is consistent for all four strains. In this reviewer's opinion the clinical significance of these differences is difficult to estimate without a study of clinical efficacy analyzed by race/ethnicity. The applicant conducted such a clinical endpoint efficacy study for their initial licensure of Flucelvax TIV: Study V58B13 was the pivotal clinical efficacy study for the original license application for Flucelvax TIV in adults 18 years and older. For mismatched strains the VE was 69% in Caucasians and 80.1% in non-Caucasians with 30 subjects having culture confirmed influenza in the Caucasians and 0 cases in non-Caucasians. There were insufficient cases of matched strain influenza infections to derive a VE for matched strains. [reference: Clinical Review of Original BLA applicaton, FDA website, http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM332069.pdf, p.34]

Baseline HI titer differences:

Table 34 shows the differences in immune response rates as a function of baseline HI antibody titers, dividing the subjects in two groups, those with baseline HI titers ≤1:10 and those with titers ≥1:10.

Table 34. Immunogenicity Results of Subjects 18 Years of Age and Above, by Baseline Immune Status, HI Assay – PPS

		HI Titers < 1:10		HI Titers ≥ 1:10	
	Day 22	**QIVc**	**TIV1c/or/TIV2c[a]**	**QIVc**	**TIV1c/or/TIV2c[a]**
A/H1N1		N = 175	N = 92	N = 1075	N = 543
	GMT (95% CI)	204.6 (158.3-264.3)	185.9 (128.6-268.8)	322.8 (300.3-347.0)	323.9 (293.5-357.4)
	HI Titer ≥ 1:40 (95% CI)	86.9% (80.9%-91.5%)	85.9% (77.0%-92.3%)	97.9% (96.8%-98.6%)	98.5% (97.1%-99.4%)
	Seroconversion Rate[b] (95% CI)	86.9% (80.9%-91.5%)	85.9% (77.0%-92.3%)	43.1% (40.1%-46.1%)	42.4% (38.2%-46.6%)
A/H3N2		N = 78	N = 40	N = 1172	N = 595
	GMT (95% CI)	98.1 (71.6-134.6)	109.3 (70.6-169.3)	406.8 (382.4-432.8)	411.3 (375.9-450.1)
	HI Titer ≥ 1:40 (95% CI)	83.3% (73.2%-90.8%)	87.5% (73.2%-95.8%)	99.4% (98.8%-99.8%)	99.3% (98.3%-99.8%)
	Seroconversion Rate[b] (95% CI)	83.3% (73.2%-90.8%)	87.5% (73.2%-95.8%)	35.3% (32.6%-38.1%)	32.1% (28.4%-36.0%)
B1		N = 73	N = 30	N = 1177	N = 605
	GMT (95% CI)	66.8 (46.8-95.3)	87.7 (52.1-147.7)	139.0 (130.8-147.7)	117.2 (107.9-127.4)
	HI Titer ≥ 1:40 (95% CI)	69.9% (58.0%-80.1%)	80.0% (61.4%-92.3%)	95.1% (93.7%-96.2%)	92.4% (90.0%-94.4%)
	Seroconversion Rate[b] (95% CI)	69.9% (58.0%-80.1%)	80.0% (61.4%-92.3%)	34.5% (31.8%-37.3%)	32.6% (28.8%-36.5%)
B2		N = 35	N = 24	N = 1215	N = 615
	GMT (95% CI)	73.9 (41.6-131.2)	89.8 (48.9-165.0)	181.8 (172.1-192.0)	167.9 (155.1-181.9)

HI Titer ≥ 1:40 (95% CI)	77.1% (59.9%-89.6%)	83.3% (62.6%-95.3%)	98.3% (97.4%-98.9%)	97.4% (95.%8-98.5%)
Seroconversion Rate[b] (95% CI)	77.1% (59.9%-89.6%)	83.3% (62.6%-95.3%)	38.7% (35.9%-41.5%)	33.5% (29.8%-37.4%)

Sources: section 5.3.5.1, CSR V130_01 Table 14.2.1.1.3, Table 14.2.1.2.3 and Table 14.2.1.3.3., pp. 475 and 561.

Abbreviations: HI = hemagglutination inhibition. PPS = per protocol set. GMT = geometric mean titer. CI = confidence interval. HI titer ≥ 1:40 = percentage of subjects with HI titer ≥ 1:40.

[a] The comparator vaccine for A/H1N1, A/H3N2 and B1 is TIV1c, for B2 the comparator vaccine is TIV2c.

[b] Seroconversion rate = percentage of subjects with either a pre-vaccination HI titer < 1:10 and post vaccination HI titer ≥ 1:40 or with a pre-vaccination HI titer ≥ 1:10 and a minimum 4-fold increase in post vaccination HI antibody titer

Reviewer Comment: Subjects with baseline HI antibody titers ≥1:10 have much higher GMTs post vaccination, and a higher percentage of these subjects achieve post vaccination HI titers ≥1:40, but these subjects do not achieve seroconversion at as high a percentage as those subjects with baseline HI antibody titers ≤1:10, for all four strains. Since all of the subjects in this study received only one influenza vaccination it appears as if having previous HI antigen exposure [either through immunization or through natural infection] allows for an enhanced immune response to the vaccine in both the TIVc and QIVc formulations. In this reviewer's opinion only a clinical efficacy endpoint study could determine if baseline HI antibody titer status influences the efficacy of an influenza vaccine.

6.2.11.4 Dropouts and/or Discontinuations

See section 6.2.10.1.3.

6.2.11.5 Exploratory and Post Hoc Analyses

N.A.

6.2.12 Safety Analyses

6.2.12.1 Methods

6.2.12.2 Overview of Adverse Events

Study V130_1 had three co-primary safety endpoints:

1. 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).
2. Percentages of subjects with unsolicited AEs were assessed from day 1 through 3 weeks after last vaccination.
3. Percentages 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.

A total 2680 subjects enrolled into the study and 2680 subjects were exposed to study vaccination. One subject, 1242013, did not receive the correct vaccine according to the randomization allocation (was randomized to QIVc group but received TIV1c vaccine) for safety analysis this subject was included in the TIV1c.

Across the 3 groups, the safety set for solicited local and systemic AEs from 30 minutes through 7 days post vaccination and safety set for unsolicited AEs from day 1 through day 22 post vaccination included (~99%) of subjects.

Twenty-eight subjects (1.0%) were excluded from the safety analysis. Twenty-seven subjects (1.0%) did not provide post vaccination solicited safety data. Seventeen subjects (0.6%) did not provide post vaccination unsolicited safety data. One subject was enrolled at 2 study sites: At site 108 the subject was enrolled (1081028) and randomized to the TIV2c group and at site 136 the subject was enrolled (1361040) and randomized to the QIVc group. Subject was discontinued at site 136 (subject did not meet entry criteria), and was followed up for safety until the end of the study at site 108. Any safety data reported from subject 1361040 was merged with that for subject1081028.

Table 35 presents the data on solicited local AEs from day 1 through day 7 after any vaccination.

Table 35. Number (%) of Subjects with Solicited Local 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**
Induration (mm)	N=1319	N=670	N=663	N=663	N=330	N=327	N=656	N=340	N=336
Any	134 (10.2%)	55 (8.2%)	60 (9.0%)	77 (11.6%)	32 (9.7%)	34 (10.4%)	57 (8.7%)	23 (6.8%)	26 (7.7%)
Severe (>100 mm)	0	1 (0.1%)	0	0	1 (0.3%)	0	0	0	0
Erythema (mm)	N=1319	N=670	N=663	N=663	N=330	N=327	N=656	N=340	N=336
Any	167 (12.7%)	80 (11.9%)	68 (10.3%)	89 (13.4%)	44 (13.3%)	33 (10.1%)	78 (11.9%)	36 (10.6%)	35 (10.4%)
Severe (>100 mm)	0	0	0	0	0	0	0	0	0
Ecchymosis (mm)	N=1319	N=670	N=663	N=663	N=330	N=327	N=656	N=340	N=336
Any	56 (4.2%)	26 (3.9%)	35 (5.3%)	25 (3.8%)	11 (3.3%)	17 (5.2%)	31 (4.7%)	15 (4.4%)	18 (5.4%)
Severe (>100	0	1 (0.1%)	0	0	1 (0.3%)	0	0	0	0

	≥18 years			≥18 to <65 years			≥65 years		
	QIVc	TIV1c	TIV2c	QIVc	TIV1c	TIV2c	QIVc	TIV1c	TIV2c
mm)									
Injection-site Pain	N=1319	N=670	N=663	N=663	N=330	N=327	N=656	N=340	N=336
Any	443 (33.6%)	186 (27.8%)	195 (29.4%)	301 (45.4%)	122 (37.0%)	133 (40.7%)	142 (21.6%)	64 (18.8%)	62 (18.5%)
Severe	3 (0.2%)	1 (0.1%)	0 (0%)	3 (0.5%)	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Source: Adapted from sBLA 125408.127, CSR for V130_01, Table 14.3.1.2. 1, pp.897-901 (for subjects ≥18 years); Table 14.3.1.2.1 , pp.906-10 (for subjects ≥18 to <65 years and ≥65 years).

Solicited AEs were reported from day 1including 30 min data through day 7.

Table 36 presents the data on solicited systemic AEs from day 1 through day 7 after any vaccination.

Table 36. Number (%) of Subjects with Solicited Systemic 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
Chills	N=1319	N=670	N=663	N=663	N=330	N=327	N=656	N=340	N=336
Any	70 (5.3%)	35 (5.2%)	36 (5.4%)	41 (6.2%)	21 (6.4%)	21 (6.4%)	29 (4.4%)	14 (4.1%)	15 (4.5%)
Severe	3 (0.2%)	3 (0.4%)	2 (0.3%)	1 (0.2%)	2 (0.6%)	0 (0.0%)	2 (0.3%)	1 (0.3%)	2 (0.6%)
Nausea	N=1319	N=670	N=663	N=663	N=330	N=327	N=656	N=340	N=336
Any	89 (6.7%)	38 (5.7%)	43 (6.5%)	64 (9.7%)	24 (7.3%)	29 (8.9%)	25 (3.8%)	14 (4.1%)	14 (4.2%)
Severe	3 (0.2%)	3 (0.4%)	5 (0.8%)	2 (0.3%)	3 (0.9%)	4 (1.2%)	1 (0.2%)	0 (0.0%)	1 (0.3%)
Myalgia	N=1319	N=670	N=663	N=663	N=330	N=327	N=656	N=340	N=336
Any	156 (11.8	80 (11.9	77 (11.6	102 (15.4	48 (14.5	49 (15.0	54 (8.2%	32 (9.4%	28 (8.3%

	≥18 years			≥18 to <65 years			≥65 years		
	QIVc	TIV1c	TIV2c	QIVc	TIV1c	TIV2c	QIVc	TIV1c	TIV2c
	%)	%)	%)	%)	%)	%)	)	)	)
Severe	6 (0.5%)	4 (0.6%)	6 (0.9%)	5 (0.8%)	3 (0.9%)	4 (1.2%)	1 (0.2%)	1 (0.3%)	2 (0.6%)
Arthralgia	N=1319	N=670	N=663	N=663	N=330	N=327	N=656	N=340	N=336
Any	90 (6.8%)	44 (6.6%)	54 (8.1%)	54 (8.1%)	27 (8.2%)	31 (9.5%)	36 (5.5%)	17 (5.0%)	23 (6.8%)
Severe	6 (0.5%)	1 (0.1%)	6 (0.9%)	3 (0.5%)	0 (0.0%)	3 (0.9%)	3 (0.5%)	1 (0.3%)	3 (0.9%)
Headache	N=1319	N=670	N=663	N=663	N=330	N=327	N=656	N=340	N=336
Any	185 (14.0%)	90 (13.4%)	89 (13.4%)	124 (18.7%)	61 (18.5%)	61 (18.7%)	61 (9.3%)	29 (8.5%)	28 (8.3%)
Severe	8 (0.6%)	5 (0.7%)	4 (0.6%)	6 (0.9%)	3 (0.9%)	2 (0.6%)	2 (0.3%)	2 (0.6%)	2 (0.6%)
Fatigue	N=1319	N=670	N=663	N=663	N=330	N=327	N=656	N=340	N=336
Any	178 (13.5%)	109 (16.3%)	81 (12.2%)	118 (17.8%)	73 (22.1%)	51 (15.6%)	60 (9.1%)	36 (10.6%)	30 (8.9%)
Severe	9 (0.7%)	2 (0.3%)	7 (1.1%)	4 (0.6%)	1 (0.3%)	5 (1.5%)	5 (0.8%)	1 (0.3%)	2 (0.6%)
Vomiting	N=1319	N=670	N=663	N=663	N=330	N=327	N=656	N=340	N=336
Any	23 (1.7%)	6 (0.9%)	5 (0.8%)	17 (2.6%)	5 (1.5%)	3 (0.9%)	6 (0.9%)	1 (0.3%)	2 (0.6%)
Severe	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
Diarrhea	N=1319	N=670	N=663	N=663	N=330	N=327	N=656	N=340	N=336
Any	77 (5.8%)	42 (6.3%)	42 (6.3%)	49 (7.4%)	25 (7.6%)	25 (7.6%)	28 (4.3%)	17 (5.0%)	17 (5.1%)
Severe	7 (0.5%	3 (0.4%	3 (0.5%	4 (0.6%	0 (0.0%	2 (0.6%	3 (0.5%	3 (0.9%	1 (0.3%

	≥18 years			≥18 to <65 years			≥65 years		
	QIVc)	TIV1c)	TIV2c)	QIVc)	TIV1c)	TIV2c)	QIVc)	TIV1c)	TIV2c)
Loss of appetite	N=1319	N=670	N=663	N=663	N=330	N=327	N=656	N=340	N=336
Any	81 (6.1%)	45 (6.7%)	39 (5.9%)	55 (8.3%)	28 (8.5%)	27 (8.3%)	26 (4.0%)	17 (5.0%)	12 (3.6%)
Severe	3 (0.2%)	1 (0.1%)	4 (0.6%)	2 (0.3%)	1 (0.3%)	3 (0.9%)	1 (0.2%)	0 (0.0%)	1 (0.3%)
Fever ≥38.0 °C	N=1319	N=670	N=663	N=663	N=330	N=327	N=656	N=340	N=336
	7 (0.5%)	5 (0.7%)	3 (0.5%)	5 (0.8%)	2 (0.6%)	1 (0.3%)	2 (0.3%)	3 (0.9%)	2 (0.6%)

Source: Adapted from sBLA 125408.127, CSR for V130_01,Table 14.3.1.2.1,pp. 913-14(for subjects ≥18 years); Table 14.3.1.2.1, pp.918-919 (for subjects ≥18 to <65 years and ≥65 years). Solicited AEs were reported from day 1including 30 min data through day 7.

Table 37 presents the unsolicited AEs by system organ classification, considered at least possibly related from day 1 through 3 weeks after last vaccination.

Table 37. Number (%) of Subjects ≥18 Years of Age with All Unsolicited Adverse Events by System Organ Classification From Day 1 Through Day 22 - Unsolicited Safety Set

Vaccine Group	QIVc	TIV1c	TIV2c
	N=1324	N=673	N=665
Any AE	213 (16.1%)	99 (14.7%)	110 (16.5%)
Blood and lymphatic system disorders	1 (0.1%)	0 (0.0%)	2 (0.3%)
Cardiac disorders	2 (0.2%)	0 (0.0%)	1 (0.2%)
Ear and labyrinth disorders	5 (0.4%)	2 (0.3%)	0 (0.0%)
Eye disorders	1 (0.1%)	2 (0.3%)	0 (0.0%)
Gastrointestinal disorders	27 (2.0%)	12 (1.8%)	7 (1.1%)
General disorders and administration site conditions	55 (4.2%)	23 (3.4%)	22 (3.3%)
Hepatobiliary disorders	1 (0.1%)	0 (0.0%)	0 (0.0%)
Immune system disorders	1 (0.1%)	0 (0.0%)	0 (0.0%)
Infections and	66 (5.0%)	32 (4.8%)	33 (5.0%)

Vaccine Group	QIVc	TIV1c	TIV2c
	N=1324	N=673	N=665
infestations			
Injury, poisoning and procedural complications	11 (0.8%)	2 (0.3%)	11 (1.7%)
Investigations	3 (0.2%)	1 (0.1%)	0 (0.0%)
Metabolism and nutrition disorders	10 (0.8%)	3 (0.4%)	3 (0.5%)
Musculoskeletal and connective tissue disorders	25 (1.9%)	13 (1.9%)	19 (2.9%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.1%)	1 (0.1%)	0 (0.0%)
Nervous system disorders	27 (2.0%)	8 (1.2%)	8 (1.2%)
Psychiatric disorders	4 (0.3%)	4 (0.6%)	0 (0.0%)
Renal and urinary disorders	1 (0.1%)	0 (0.0%)	4 (0.6%)
Reproductive system and breast disorders	5 (0.4%)	1 (0.1%)	2 (0.3%)
Respiratory, thoracic and mediastinal disorders	39 (2.9%)	23 (3.4%)	19 (2.9%)
Skin and subcutaneous tissue disorders	8 (0.6%)	9 (1.3%)	7 (1.1%)
Surgical and medical procedures	2 (0.2%)	1 (0.1%)	2 (0.3%)
Vascular disorders	4 (0.3%)	2 (0.3%)	2 (0.3%)

Source: Adapted from sBLA 125408.127, CSR for V130_01, Table 14.3.1.13.1, p. 1381-82.
Abbreviation: AE-adverse events.

Table 38. Number (%) of Subjects ≥18 to <65 Years of Age and ≥65 Years of Age with Unsolicited Adverse Events After Vaccination- Unsolicited Safety Set

	≥18 to <65 years			≥65 years		
	QIVc	TIV1c	TIV2c	QIVc	TIV1c	TIV2c
	N=665	N=330	N=328	N=659	N=343	N=337
Any AE	212 (31.9%)	88 (26.7%)	107 (32.6%)	282 (42.8%)	155 (45.2%)	144 (42.7%)
Possibly or probably related AE	28 (4.2%)	9 (2.7%)	15 (4.6%)	29 (4.4%)	13 (3.8%)	15 (4.5%)
SAE	11	6 (1.8%)	5 (1.5%)	41	16	16

	(1.7%)			(6.2%)	(4.7%)	(4.7%)
Possibly or probably related SAE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AE leading to premature withdrawal from study	0 (0.0%)	0 (0.0%)	1(0.3%)	2 (0.3%)[a]	1(0.3%)	0 (0.0%)
Medically attended AE	141 (21.2%)	58 (17.6%)	67 (20.4%)	203 (30.8%)	114 (33.3%)	99 (29.4%)
NOCD	24 (3.6%)	10 (3.0%)	12 (3.7%)	38 (5.8%)	15 (4.4%)	17 (5.0%)
Death	0 (0.0%) N=674	0 (0.0%) N=334	1 (0.3%) N=332	5 (0.8%) N=661	5 (1.5%) N=342	1 (0.3%) N=337

Source: Adapted from sBLA 125408.127, CSR for V130_01,Table 14.3.1.13.2; Table14.3.1.18.2; Table 14.3.2.2.2; Table 14.3.2.3.2; Table 14.3.2.4.2; Table14.3.2.6.2; Table 14.3.2.5.2; Table14.3.2.1.2.,pp. 1406-2202.
AE: adverse event; SAE: serious adverse event, NOCD: new onset chronic disease.

6.2.12.3 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). None of these events have been considered as related to the vaccine by the investigator or this clinical reviewer. Table 39 presents the data on the deaths in the study categorized by subject number, cause of death, and relationship to vaccine.

Table 39. All Deaths in Study V130-01

Subject Number/sex/race	Cause of death	Relationship to Vaccine
110/1102012/76/ M/WHITE	ACUTE CARDIAC FAILURE	None
111/1112027/74/ F/WHITE	MYOCARDIAL INFARCTION	None
124/1242004/67 M/WHITE	CARDIAC ISCHEMIA	None
126/1262011/81 M/WHITE	HEMOPHAGOCYTIC SYNDROME	None
131/1312017/74/ M/WHITE	BILATERAL SUBDURAL HEMATOMAS	None
102/1022057/72/ M/WHITE	CARDIAC ARREST	None

103/1032012/89/ M/WHITE	FATAL CARDIAC ARREST	None
107/1072020/71/ F/WHITE	SEPSIS	None
121/1212020/67/ F/WHITE	DEATH OF UNKNOWN CAUSE	None
103/1031002/64/ M/WHITE	CARDIAC ARREST	None
131/1312031/83/ M/BLACK	CONGESTIVE HEART FAILURE	None
124/1242030/73/ F/WHITE	ATRIAL FIBRILLATION	None

Source: Adapted from sBLA 125408.127, CSR for V130_01, Table 14.3.2.11, p.2860.

6.2.12.4 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). All the SAEs were judged by the investigator as 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 elderly.

6.2.12.5 Adverse Events of Special Interest (AESI)

N.A.

6.2.12.6 Clinical Test Results

N.A.

6.2.12.7 Dropouts and/or Discontinuations

See section 6.2.10.1.3.

6.2.13 Study Summary and Conclusions

Study V130_01 met both of the co-primary immunogenicity endpoints and all three of the secondary immunogenicity endpoints. The safety profile did not reveal any safety signals.

9 Additional Clinical Issues

9.1.1 Human Reproduction and Pregnancy Data

There were 12 pregnancies confirmed in the study with two therapeutic abortion outcomes and no data available on the other ten pregnancies. [Source: CSR V130_01, listings 16.2.5.6 and 16.2.5.7, pp. 2372-2377].

9.1.3 Pediatric Use and PREA Considerations

In accordance with the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), the requirement for studies in children from birth to <6 months of age was waived because vaccination with Flucelvax QIV in infants <6 months of age would provide no meaningful therapeutic benefit over initiating vaccination at 6 months of age, and Flucelvax QIV is not likely to be used in a substantial number of infants < 6 months of age. A study in children 6 months to <4 years of age was deferred because the product is ready for approval in individuals 4 years of age and older.

9.1.4 Immunocompromised Patients

Flucelvax QIVc has not been studied in immunocompromised patients.

9.1.5 Geriatric Use

See section 6.2 (study V130_01) of this clinical review.

10. CONCLUSIONS

In study V130_01, the effectiveness of Flucelvax QIV in adults 18 years and older was inferred by demonstrating that the HI antibody responses following Flucelvax QIV vaccination were non-inferior to HI responses for the corresponding strains in Flucelvax [trivalent], based on the ratio of GMTs and seroconversion rates. There were no safety signals identified in the study and the local and systemic adverse events were consistent with those seen in other seasonal influenza vaccines.

Study V130_03: The secondary objective to demonstrate that QIVc met seroconversion criteria and the criteria for the percentage of subjects achieving HI titers ≥1:40 per CBER criteria was most relevant to support accelerated approval of Flucelvax QIV in children 4 to <18 years of age. In subjects who received Flucelvax QIV, the CBER criteria for the secondary endpoints were met all four influenza vaccine strains; the lower bound of the 95% CI (LBCI) for the seroconversion rates were ≥40% and the percentages of subjects who achieved a post-vaccination HI titer ≥1:40 were ≥70% (95%LBCI).

In study V130_03, the effectiveness of Flucelvax QIV in children 4 to <18 years of age, using the traditional approval pathway, cannot be inferred by noninferiority comparisons of HI antibody responses to Flucelvax TIV because

the clinical benefit of Flucelvax TIV has not been demonstrated in a confirmatory study yet. However, the immunogenicity data in subjects who received Flucelvax QIV did support accelerated approval, as described in the FDA Guidance for Industry “Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines”, of QIV in children 4 to <18 years of age for the seroconversion rates were ≥40% and the percentages of subjects who achieved a post-vaccination HI titer ≥1:40 were ≥70% (95%LBCI). In accordance with accelerated approval regulations, a confirmatory study will be conducted in the post marketing period to verify and further describe the clinical benefit via demonstration Flucelvax QIV clinical efficacy to prevent influenza disease (clinical endpoint) in children 4 to <18 years of age.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

The following Table summarizes the risk and benefit considerations for Flucelvax.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• .Influenza infects 5-20% of the population each year with a wide range of severity, including up to 200,000 hospitalizations, 3,000-44,000 deaths in the US annually • - Morbidity/mortality highest among the very young, the elderly, and those with underlying medical conditions • - Roughly 10% of hospitalizations result in death, mostly in elderly • - Since the late 1980s, two antigenically distinct B virus lineages have circulated, sometimes concurrently; • - Influenza can cause pandemics	• - Influenza is a significant cause of morbidity/mortality in the US • - A proportion of infections result in serious or life-threatening disease, particularly among high-risk groups • - Illnesses caused by influenza B viruses represent a proportion of overall influenza disease burden
Unmet Medical Need	• - The neuraminidase inhibitor class of antivirals are available for post-exposure chemoprophylaxis; however, they must be given twice daily; are only available in oral and inhaled formulations; and provides protection only during the time when administered • - Resistance to one class of antivirals is now widespread, and strains resistant to oseltamivir have circulated widely in the past • - Trivalent influenza vaccines containing one A/H1N1 strain, one A/H3N2 strain, and one B strain have been available since 1980 • -The effectiveness of inactivated influenza vaccines has been estimated to be approximately 59%, and there is an extensive record of safety • - Vaccine effectiveness is lower among the very young, the elderly, and among those with certain chronic underlying medical conditions; and is lower in situations of antigenic mismatch • - Trivalent influenza vaccines contain one influenza B strain; this strain has been optimally matched to the lineage of the circulating viruses only half the time in the past 13 years; modeling studies suggest a moderate reduction in cases if both B lineages are included in a quadrivalent vaccine, depending on B virus incidence, vaccine effectiveness, and vaccine supply for the specific season • - There is only influenza vaccine approved for children as young as 6 months of age.	• Antivirals are effective for influenza prevention, but are operationally difficult to use, and resistance is a frequent concern • The same antivirals that could be used for influenza prevention are used to treat active infection and widespread use for prevention could risk fewer drugs available for treatment if resistance patterns emerge and spread • - Currently licensed influenza vaccines are effective against antigenically matched strains, and are well tolerated • -This will be the first cell-based Quadrivalent seasonal influenza vacine • - Inclusion of both B lineages as part of a quadrivalent vaccine is projected to provide additional benefit in most seasons • - There are only two currently licensed quadrivalent influenza vaccines, and

		neither are approved for children 6 through 23 months of age
Clinical Benefit	• - Two trials evaluating safety and immunogenicity were submitted in this supplement, one in adults ≥18 years of age and older, one in children ≥4 years to <18 years of age. The trials compared the quadrivalent vaccine to two trivalent formulations, each containing one of the two B lineages included in the quadrivalent vaccine. • - Both trials included a comparator group (Flucelvax TIV), and designed with CBER advice • - Effectiveness was demonstrated using hemagglutination inhibiting (HI) titers; the quadrivalent vaccine was compared to an active control, Flucelvax trivalent vaccine, as measured by the GMT ratio and the difference in seroconversion rates as co-primary endpoints, adapted from criteria developed for the accelerated approval of seasonal trivalent influenza vaccines. • - The Flucelvax Quadrivalent met all immunologic criteria for non-inferiority against all four strains compared to trivalent vaccines in all ages studied; and met the secondary non-inferiority and superiority criteria based on CBER agreement.	• Flucelvax QIVc effectiveness, inferred from a serological marker of protection (HI antibody), was demonstrated for age groups 18 years of age and older. For children 4 to <18 years of age, HI antibody was viewed by CBER as a surrogate reasonably likely to predict clinical benefit. • These immunogenicity results indicate that Flucelvax QIVc is effective against influenza similar to that provided by Flucelvax TIV in individuals 18 years and older for the strains common to both vaccines, and additional protection for the alternate B lineage over that provided by the trivalent vaccine.
Risk	• . Flucelvax trivalent vaccines have a three year record of safety • - As recommended by CBER, a total of 5,012 individuals exposed to the vaccine comprise the safety database for Flucelvax Quadrivalent • - The most substantial risks of vaccination with Flucelvax Quadrivalent identified in clinical trials are associated with local adverse reactions at the injection site, observed in all age groups. • - Systemic adverse reactions, including fever, malaise, and irritability, were common in influenza-naïve young children, but none of these reactions resulted in a serious adverse event (such as hospitalization or febrile seizure) among those receiving Flucelvax Quadrivalent. • - Most solicited adverse reactions were mild in severity, and all resolved within a small number of days without sequelae • - New onset neurologic disorders and other specifically monitored serious adverse events did not occur at an increased frequency among Flucelvax	• The safety database is of adequate size to support licensure • - The risks of vaccination with Flucelvax Quadrivalent appear to be minor, and similar to that associated with trivalent Flucelvax • - Safety was not evaluated in pregnant women and nursing mothers

	Quadrivalent recipients; no other safety signals were identified in the trials submitted in the supplement	
Risk Management	• The most common adverse reactions following vaccination with Flucelvax Quadrivalent, including local injection site reactions and systemic reactogenicity, are mild and self-limited • - High-quality data regarding the risks of influenza vaccination in pregnant women are limited, but the evidence available in the literature to date does not indicate that there is a safety signal.	• The risks observed in the trials submitted in support of Flucelvax Quadrivalent licensure will be summarized in the package insert. Routine pharmacovigilance is recommended.

11.2 Risk-Benefit Summary and Assessment

In individuals 18 years and older, the HI antibody responses following Flucelvax QIV vaccination were non inferior compared to responses for corresponding strains in the licensed trivalent influenza vaccine, and superiority of HI responses to influenza B strains in comparison to alternate lineages not present in the trivalent vaccine were demonstrated. No new safety signals were identified, and the safety profile of QIV is similar to the safety profile of trivalent Flucelvax. The observed adverse reactions following vaccination of Flucelvax QIV were minimal and self-limited, and will be described adequately in the package insert. In the opinion of this reviewer the data submitted in this BLA supplement indicate Flucelvax QIV presents a favorable overall risk-benefit profile for persons ages 4 years of age and older.

11.3 Discussion of Regulatory Options

Use of a serological marker of protection (HI antibody) is viewed by CBER as an acceptable regulatory approach to infer effectiveness of new influenza vaccines, and has been an approach used to demonstrate effectiveness for other influenza vaccines licensed in the US given the shortage of flu vaccines.

Individuals 4 to <18 years of age

The applicant chose to use Flucelvax trivalent influenza vaccine as the comparator in study V130_03, which enrolled individuals 4 to <18 years of age. At the time the study was conducted, Flucelvax TIV vaccine was not licensed in the US for this age group.

- The applicant was advised by CBER, at the time that the protocol was submitted to the IND, that there was inherent risk in using a non-US licensed influenza vaccine as the comparator vaccine because the study results might not support the effectiveness of Flucelvax QIV, via the regulatory pathway for 'traditional' approval, if QIV antibody responses were compared to a vaccine for which data confirming vaccine effectiveness in the corresponding age group had not previously been reviewed and approved by FDA.
- The immunogenicity data from study V130_03 do support extending the use of Flucelvax QIV, via the accelerated approval regulations, to children 4 years to <18 years of age, for reasons described in the CBER Guidance for Industry document entitled "Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines".

Individuals 18 years and older

- Study V130_01 includes Flucelvax TIV as the comparator vaccine. Since Flucelvax TIV was approved by FDA for use in adults 18 years and older based on an clinical efficacy study, demonstration of immunological non-inferiority of HI antibody responses following Flucelvax QIV vaccination to corresponding influenza type-specific antibody responses following Flucelvax TIV vaccination was an acceptable regulatory approach to demonstrating

effectiveness of Flucelvax QIV in this age group, via the 'traditional' licensure pathway.

In a Type A meeting held 19 October 2015, CBER discussed with the applicant about the possibility of using the AA pathway as a licensure approach for demonstrating the safety and effectiveness of Flucelvax QIVc and Flucelvax TIV. For both vaccines, HI antibody response, evaluated by the GMTs and percentages of subjects achieving a HI titer ≥1:40 at three weeks post vaccination, is an acceptable surrogate reasonably likely to predict clinical benefit. The applicant proposed this approach using AA of QIVc for 4-<18 year olds and CBER concurred. In accordance with the accelerated approval regulations, a confirmatory study to further verify and describe the clinical benefit of Flucelvax QIV is required.

11.4 Recommendations on Regulatory Actions

The safety and immunogenicity data support approval of Flucelvax QIV in individuals 18 years and older using the traditional approval pathway and in individuals 4 to <18 years of age in accordance with the accelerated approval regulations.

11.5 Labeling Review and Recommendations

The label was reviewed and recommendations were communicated to the applicant, and all issues were adequately addressed. The main changes were for the (a) Indications and Usage and (b) inclusion of the following language to indicate that, for individuals ages 4 years to <18 years, approval was based on a biological marker for the accelerated approval pathway: "For children and adolescents 4 to <18 years of age, approval is based on the immune response elicited by FLUCELVAX QUADRIVALENT. Data demonstrating a decrease in influenza disease after vaccination of children and adolescents 4 to <18 years of age with FLUCELVAX QUADRIVALENT are not available." sections 6 and 14 were updated with data from studies V130_01 and V130_03.

11.6 Recommendations on Post marketing Actions

The post-marketing requirements include the following studies:

- In accordance with the accelerated approval regulations, a confirmatory clinical endpoint efficacy study (V130_12) will be conducted in children 4 to <18 years of age to verify and further describe the clinical benefit of Flucelvax QIV.

- A safety and immunogenicity study (V130_10) in children 6 months to <4 years of age will be conducted to fulfill PREA requirements.

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