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BLA Clinical Review Memorandum

Application Type	Efficacy Supplement
STN	125408.351
CBER Received Date	December 14, 2020
PDUFA Goal Date	October 14, 2021
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Jonathan Albert, MD
Review Completion Date / Stamped Date	October 14, 2021
Supervisory Concurrence	Rebecca Reindel, MD CRB2 Team Leader Andrea Hulse, MD CRB2 Branch Chief
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	Suspension; intramuscular injection
Dosing Regimen	6 months through 23 months of age: one dose, or, two doses administered at least 4 weeks apart, depending upon prior influenza immunization.
Indication(s) and Intended Population(s)	Active immunization in persons 6 months through 23 months of age 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

AA	Accelerated Approval
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
BIMO	Bioresearch Monitoring Committee
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CMI	cell-mediated immunity
COVID-19	Coronavirus Disease 2019
CSF	cerebrospinal fluid
CSR	clinical study report
DMC	data monitoring committee
DVRPA	Division of Vaccines and Related Product Applications
ES	Executive Summary
FAS	Full Analysis Set
GMR	geometric mean ratio
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutination inhibition assay
ICSR	Individual Case Safety Report
IEC	Independent Ethics Committee
IR	information request
IRB	Institutional Review Board
LLOQ	lower limit of quantification
MAAE	medically attended adverse event
MDCK	Madin-Darby canine kidney
MedDRA	Medical Dictionary for Regulatory Activities
MN	microneutralization
NA	neuraminidase
NOCD	new onset chronic disease
OBE	Office of Biostatistics and Epidemiology
OVRR	Office of Vaccines Research and Review
PCR	polymerase chain reaction
PMC	postmarketing commitment
PMC	postmarketing commitment
PMM	pattern-mixture model
PMR	postmarketing requirement
PPS	Per Protocol Set
PREA	Pediatric Research Equity Act
PVP	pharmacovigilance plan
QIV	Afluria Quadrivalent
QIVc	Flucelvax Quadrivalent
SAE	serious adverse event
sBLA	supplemental biologics license application
SEB	staphylococcal enterotoxin B
SCR	seroconversion rate
STN	submission tracking number
TIVc	Flucelvax Trivalent

1. Executive Summary

Flucelvax Quadrivalent (QIVc) is an inactivated seasonal influenza vaccine containing antigens from two influenza A subtype viruses (H1N1 and H3N2) and two influenza type B viruses. QIVc was approved for use in persons 4 years of age and older on 23 May 2016 through STN 125408/127 in accordance with the regulations for Accelerated Approval (AA; 21 CFR 601.40-46) based on data from Study V130_03 that included 2,333 children 4 through 17 years of age. This study demonstrated noninferior immunogenicity and comparable safety to Flucelvax (trivalent) vaccine, which was itself approved for use in children 4 through 17 years of age under Accelerated Approval provisions. Subsequently, QIVc was granted full approval for use in children 2 through 17 years of age based on a data from a successful clinical endpoint efficacy trial. The Applicant (Seqirus, Inc) submitted a supplemental biologics license application (sBLA), STN 125408/351, on 14 December 2020 which provides clinical data from Study V130_10 to support extending use of QIVc down to children 6 months of age for the prevention of influenza disease caused by influenza A subtypes and type B viruses contained within the vaccine. This sBLA satisfies Pediatric Research Equity Act (PREA) postmarketing study requirement (PMR) #2 for QIVc.

Immunogenicity
Study V130_10, "A Phase 3, Randomized, Observer-Blind, Multicenter, Noninferiority Study to Evaluate Safety and Immunogenicity of a Cell-based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) and a United States-licensed Quadrivalent Influenza Virus Vaccine (QIV) in Healthy Subjects 6 Months Through 47 Months," was intended to demonstrate that one or two doses of QIVc elicits an immune response that is non-inferior to that of a quadrivalent vaccine (QIV; Afluria) containing the recommended strains for that season, in subjects 6 months through 47 months. Immunogenicity was measured by geometric mean titers (GMTs) and seroconversion rates (SCRs) at Day 29 for previously vaccinated subjects or Day 57 for vaccine-naïve subjects, using hemagglutination inhibition assay (HAI) for influenza strains A/H1N1, B/Yamagata, and B/Victoria, or microneutralization (MN) assay for influenza strain A/H3N2. Both assays used for the primary endpoint analyses used cell-derived target viruses. The predefined success criteria required that the upper bounds of the two-sided 95% confidence intervals of the Day 29/57 GMT ratios not exceed 1.5, and the upper bounds of the 95% confidence intervals of the Day 29/57 differences in seroconversion rates not exceed 10%. Postvaccination GMT ratios with 95% confidence intervals for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria were 0.73 (0.65, 0.84), 1.04 (0.93, 1.16), 0.73 (0.66, 0.81), and 0.88 (0.79, 0.97), respectively. Postvaccination seroconversion rate differences with 95% confidence intervals for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria were -11.46% (-16.45, -6.42), 3.13% (-1.44, 7.81), -14.87% (-19.61, -9.98), -5.96% (-10.33, -1.44), respectively. These results meet the predefined primary immunogenicity endpoint success criteria. These results support the effectiveness of QIVc for the prevention of influenza disease caused by influenza virus subtypes A and B contained in the vaccine in children 6 months through 47 months of age.

Safety
No new safety signals were identified following the review of safety data from V130_10. The most frequent local solicited adverse reactions during this study were tenderness and erythema of the injection site, which were reported in 27.9% and 25.8% of QIVc recipients, respectively, and 30.0% and 24.6% of comparator recipients, respectively. The most frequent systemic solicited adverse reactions were irritability and sleepiness,

which were reported 27.9% and 26.9% of QIVc recipients, respectively, and 29.6% and 25.5% of comparator recipients, respectively. The proportion of subjects with at least one serious adverse event (SAE) was 0.9% in both treatment groups. No SAE was considered related to the investigational product by the Applicant or by this reviewer. There were no deaths in the comparator groups and two deaths among QIVc recipients: one subject died in a motor vehicle accident and one subject died from complications secondary to status epilepticus thought to be caused by adenovirus encephalitis. Neither of these deaths were considered related to the study vaccination by the Applicant or by this reviewer.

Pediatric Assessment and Pediatric Research Equity Act
Study V130_10 was a deferred pediatric study that was conducted in children 6 months through 47 months of age under the PREA after Accelerated Approval was granted for QIVc in children 4 years of age and older. The results of V130_10 were submitted in this sBLA to fulfill the outstanding PREA postmarketing requirement and to support approval of QIVc for use in children as young as 6 months of age.

Pharmacovigilance Plan
The Applicant is planning routine pharmacovigilance activities for continued assessment of QIVc including surveilling for the Important Identified Risk of anaphylaxis and the following Important Potential Risks, which were included in the Risk Management Plan as plausible class effects: convulsions, Guillain-Barre syndrome, demyelination, vasculitis, and immune thrombocytopenic purpura. The Applicant's proposed pharmacovigilance plan (PVP) is adequate.

Reviewer comment: *There were no specific safety events related to QIVc that prompted the inclusion of vasculitis, immune thrombocytopenic purpura, or convulsions in the PVP. In general, "important potential risks" are selected based on the safety profile of products in the same class, or are based on a mechanistic basis of risk related to the investigational product.*

Recommendation
The safety and immunogenicity results of Study V130_10 support extension of the approved indication down to 6 months of age.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Table 1. Demographics of Participants Enrolled in V130_10 and Evaluated for Safety and Immunologic Response to the Vaccine

Demographic Characteristic	**QIVc (n=1597)**	**QIV (n=805)**
Mean Age in Months (SD)	28.1 (11.54)	28.2 (11.63)
Age Group:		
6 months through 23 months (%)	595 (37.3)	299 (37.1)
24 months through 47 months (%)	1002 (62.7)	506 (62.9)
Sex Ratio M:F (%)	803:794 (50.3:49.7)	406:399 (50.4:49.6)
Racial Origin (%):		
White	1039 (65.1)	539 (67)
Black or African American	455 (28.5)	209 (26)
Asian	13 (0.8)	8 (1.0)

Demographic Characteristic	QIVc (n=1597)	QIV (n=805)
Native Hawaiian or Other Pacific Islander	8 (0.5)	6 (0.7)
American Indian or Alaska Native	11 (0.7)	11 (1.4)
Other	71 (4.4)	32 (4.0)
Ethnic Origin (%):		
Hispanic	434 (27.2)	226 (28.1)
Not Hispanic or Latino	1160 (72.6)	575 (71.4)
Not Reported	3 (0.2)	1 (0.1)
Body Mass Index (kg/m^2)		
Mean (SD)	16.99 (2.47)	17.15 (3.0)
Median	16.73	16.75
Previous Influenza Vaccination (%):		
Previously Vaccinated	810 (50.7)	430 (53.4)
Not Previously Vaccinated	787 (49.3)	375 (46.6)

Source: Adapted from STN 125408/351, Clinical Study Report V130_10, Table 10-6, p. 87

Subgroup Immunogenicity Analysis
Subjects from the younger age group (i.e., 6 months through 23 months) appeared to have lower GMT responses and seroconversion rates compared to subjects from the older age group (24 through 47 months) after receiving either QIVc or QIV. This difference in immunogenicity was balanced between study arms. These age-dependent differences were observed for each of the four strains of influenza tested in V130_10. Of note, subjects from the younger age group demonstrated comparable immunogenic responses to QIVc and QIV. Please see Section 6.1.11.3 of this review for further discussion of subgroup analyses of immunogenicity.

Subgroup Safety Analysis
The rate of solicited systemic adverse reactions was higher in the younger age group than the older age group after receipt of either QIVc or U.S.-licensed QIV. This difference was balanced between treatment arms of the study, and the overall rate of solicited adverse reactions was similar between age groups in V130_10.

The rate of vaccine reactogenicity (defined as a report of at least one solicited adverse reaction from Day 1 through Day 7) appeared to be slightly higher in subjects who are Native Hawaiian/Pacific Islander (n=14) or American Indian/Alaska Native (n=22) with 71.4% and 72.7% of subjects experiencing at least one solicited adverse reaction, respectively, compared to 60.9% of subjects overall. However, these rates are based on very small samples sizes and analyses were not adequately powered to detect differences in vaccine reactogenicity with respect to race.

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	

☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Influenza infection in the United States is characterized by seasonal epidemics, usually occurring during the winter months. During the years 2010-2020, annual deaths due to influenza illness in the United States ranged from 12,000 to 61,000.[5] The rates of infection are highest among children, but serious illness and death are reported more frequently among persons of any age who have chronic underlying medical conditions (as defined by the Advisory Committee on Immunization Practices) that place them at increased risk of complications. Influenza vaccination is the primary method for preventing influenza illness and its severe complications.[2] In certain circumstances, antiviral medications such as oseltamivir play an important role in preventing medical complications related to influenza as well as post-exposure chemoprophylaxis for influenza.

The Advisory Committee on Immunization Practices (ACIP) recommends annual influenza vaccination for all persons 6 months of age and older. Children 8 years of age and younger who are not previously vaccinated against influenza require a second dose of influenza vaccine 28 days after the initial dose. The ACIP recommends additional support programs to promote vaccination of persons at high risk of influenza-related complications, including persons 50 years of age and older, children 6 months of age and older, healthcare workers, and persons with chronic medical conditions.[6]

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

Prevention of infection with influenza may be achieved through various means, including avoidance of contact with respiratory droplets (e.g., use of a face mask), hand washing, distancing from infected persons, and pre-exposure chemoprophylaxis using neuraminidase (NA) inhibitors.

There are four FDA-approved antiviral drugs recommended by CDC for the 2020 influenza season: oseltamivir phosphate (available as a generic version or under the trade name Tamiflu), zanamivir (trade name Relenza), peramivir (trade name Rapivab), and baloxavir marboxil (trade name Xofluza). Because of widespread resistance, two older adamantane agents, amantadine and rimantidine, are no longer recommended for use against seasonal influenza viruses. Oseltamivir, zanamivir, and permivir are main NA inhibitors. On October 24, 2018, FDA approved baloxavir marboxil, which has a different mechanism of action than adamantanes and NA inhibitors. Baloxavir is an oral agent which inhibits the endonuclease activity of the polymerase acidic protein, an enzyme within the viral RNA polymerase complex required for influenza A and B viral gene transcription and replication.

One of three NA inhibitors, oseltamivir, is an oral antiviral indicated for the treatment of influenza A and B in persons ≥14 days of age and for chemoprophylaxis in persons ≥1 year of age. Frequent gastrointestinal side effects may limit its usefulness. Zanamivir, another NA inhibitor, is indicated for treatment of influenza in persons ≥7 years of age and for chemoprophylaxis in persons ≥5 years of age. It is administered as an orally inhaled powder and is associated with bronchospasm especially in persons with underlying asthma or chronic obstructive pulmonary disease. The third NA inhibitor, peramivir, is a single-dose intravenous antiviral indicated only for the treatment of acute uncomplicated influenza A and B infection in persons ≥2 years. Adverse effects include diarrhea. Postmarketing reports for NAs have also described serious cutaneous reactions and sporadic transient neuropsychiatric events. Emergence of resistance to oseltamivir during treatment of seasonal influenza is well described and has also been reported in persons receiving oseltamivir for H5N1 infection. Zanamivir is much less frequently associated with resistance even in oseltamivir-resistant viruses. Overall, however, potential resistance and drug toxicities limit the use of antiviral agents and illustrate the need for effective prophylactic vaccines.[2, 3, 4, 6, 7, 10] Baloxavir is indicated for the treatment of acute uncomplicated influenza in persons 12 years of age and older who have been symptomatic for no more than 48 hours. In October 2019, the indication was expanded to specifically include persons 12 years of age and older who are at high risk for complications of influenza. As with other antiviral agents, emergence of resistance may occur during treatment.[1, 8, 14]

Overall, drug toxicities, potential resistance, and age restrictions limit the use of antiviral agents for the treatment and prevention of seasonal influenza infections and illustrate the need for effective prophylactic vaccines.

2.3 Safety and Efficacy of Pharmacologically Related Products

There are currently 18 U.S.-licensed polyvalent seasonal influenza vaccines (10 trivalent vaccines, 8 quadrivalent vaccines), including Flucelvax QIV. Fourteen of these vaccines are egg-based inactivated vaccines; two are live, attenuated vaccines; two are cell-based vaccines. Each of these vaccines is licensed for the indication of prevention of

influenza infection for the strains contained within the vaccine. Influenza vaccines currently licensed for children 6 months and older include Afluria Quadrivalent, Afluria Trivalent, Flulaval Trivalent, Flulaval Quadrivalent, Fluzone Trivalent, Fluzone Quadrivalent, and Fluarix.

The most common solicited adverse reactions following influenza vaccination are injection site pain, headache, fatigue, and myalgia. Syncope can occur immediately following administration of injectable vaccines, including Flucelvax. Syncope may be associated with transient neurological signs such as visual disturbances, paresthesias, and tonic-clonic limb movements. Hypersensitivity reactions, including anaphylaxis, are uncommon.

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

The first approval of QIVc for marketing was in the United States on 23 May 2016[12] (international birth date) and it is currently approved in 36 countries as of 24 August 2020, including United States, Canada, Europe (28 EU countries, plus Iceland, Norway and Lichtenstein), Taiwan, Brazil, and Australia. Over 6,000 subjects have been exposed to QIVc in the 4 completed studies of the QIVc clinical development program. The cumulative post marketing exposure since the first approval of QIVc is estimated to be approximately 116.2 million vaccinated persons. The following adverse events have been identified using postmarketing surveillance of QIVc:

Immune system disorders: Allergic or other immediate hypersensitivity reactions, including anaphylactic shock.

Nervous system disorders: Syncope, presyncope, paresthesia.

Skin and subcutaneous tissue disorders: Generalized skin reactions including pruritus, urticaria, or non-specific rash.

General disorders and administration site conditions: Extensive swelling of the injected limb.

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

Flucelvax Trivalent (TIVc) was licensed for use in adults in the United States in 2012 and was subsequently given Accelerated Approval (AA) for children 4 through 17 years of age. Flucelvax Quadrivalent (QIVc) was licensed for use in adults in the United States in 2016, and the AA postmarketing requirement (PMR) for TIVc to confirm clinical benefit in children 4 through 17 years of age was transferred to QIVc. Full approval of QIVc was extended to children 2 years of age and older on 3 March 2021.

A chronological summary of the major regulatory activity related to this submission is listed below:

May 2016:
FDA granted licensure via the AA pathway for use of QIVc in children 4 years through 17 years of age in May 2016. The clinical data supported “traditional” approval for adults 18 years and older. Studies V130_12 and V130_10 were PMRs for this approval, to

evaluate safety and effectiveness in ages 4 through 17 years (AA PMR) and 6 months to <4 years (PREA PMR), respectively.

August 2018:
Version 2.0 of the protocol for V130_10 was submitted, including the following key amendments:

- Incorporation of the Center for Biologics Evaluation and Research (CBER) request that noninferior immune responses be assessed for all 8 co-primary endpoints, using MN assay data for the co-primary endpoints related to the A/H3N2 strain in addition to hemagglutination inhibition assay (HAI) assay data for the co-primary endpoints related to the A/H1N1, B/Yamagata, and B/Victoria strains.
- The secondary immunogenicity objectives were revised to specify that cell-derived target viruses would be used for the HAI and MN assays, and an exploratory immunogenicity objective was added to assess vaccine responses using egg-derived target viruses for the HAI and MN assays.
- Confirmation that Afluria was to be used as the U.S.-licensed comparator vaccine.
- Blood volume requirements were confirmed for subjects enrolled in the cell-mediated immunity (CMI) population.

IND 15744 was placed on partial clinical hold in August 2018 because the V130_10 study design was deficient to meet its stated objectives as the proposed microneutralization (MN) assay used to measure the primary study endpoints for the A/H3N2 vaccine component had not been validated for its intended use, and a strong correlation of MN titers with HAI titers had not been adequately demonstrated. Additionally, CBER did not agree that the proposed seroconversion definition and geometric mean titer (GMT) ratio primary endpoint were appropriate as the basis for prespecifying success criteria for the A/H3N2 vaccine component and requested the rationale and data to support the proposed seroconversion definition as well as a revision of the NI margin to 1.5 for the GMT comparison of QIVc with U.S.-licensed quadrivalent influenza virus vaccine (QIV, trade name Afluria Quadrivalent) using a GMT ratio =1 for sample size calculations.

October 2018:
CBER provided responses to requests for advice regarding validation of the MN assay.

February 2019:
A complete response to partial clinical hold, including a revised study synopsis for V130_10, was submitted to the IND. Partial clinical hold was removed after the clinical review of the proposed primary endpoint and CMC and statistical review of the MN assay validation reports and the biostatistical comparability report submitted by the Applicant. The primary immunogenicity endpoints were adapted for the MN assay results using egg-based target viruses; however, data to support the validation of the MN assay using cell-based target viruses were not yet submitted.

July 2019:
Version 3.0 of the V130_10 protocol was submitted, with the following key revisions:

- Specification that cell-derived target viruses would be used for the HAI and MN assays for the primary immunogenicity endpoints.

- Specification that the secondary immunogenicity objectives using both cell-derived and egg-derived target viruses for the HAI and MN assays will be done for the entire subject population, rather than just a subset.
- Revision of protocol to use MN assay for primary immunogenicity analyses for strain A/H3N2 (please see Section 2.5 above for details).
- Addition of an exploratory endpoint to assess the immunogenicity of A/H3N2 using the HAI assay.
- Separation of the CMI population as a separate group rather than a subset of the FAS Immunogenicity Group given the high blood volume requirements to conduct assays for both immunogenicity endpoints.

September 2019:
The Applicant submitted data to expand the MN assay range to include cell-based target viruses and Study V130_10 was initiated.

December 2019:
The MN assay using cell-based target viruses was validated for assessment of primary immunogenicity endpoints for influenza strain A/H3N2 and Version 4.0 of the V130_10 protocol was submitted, with the following key revisions:

- Addition of Procedures for Database Lock and Unblinding of Randomization Code at the end of the treatment period
- Primary and secondary immunogenicity endpoints would be assessed once all subject have completed the treatment period (i.e., all immunogenicity assays have been collected from all study subjects).

December 2020:
Current sBLA submitted with data from Study V130_10 to evaluate the safety and effectiveness of QIVc to satisfy PREA PMR #2 for the age group 6 months through 23 months of age.

March 2021:
Full approval for Flucelvax Quadrivalent was granted in children 2 through 17 years of age based on data submitted from Study V130_12 through sBLA STN 125408/329, which partially fulfilled PMR #2.

August 2021:
Study V130_10 results presented to the Pediatric Research Committee. The committee agreed with the conclusion of the Division of Vaccines and Related Products Applications that the safety and immunogenicity data support approval of QIVc for the proposed indication in children 6 months through 23 months of age.

2.6 Other Relevant Background Information

Not applicable.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Phase 3 Study V130_10 was conducted in accordance with Good Clinical Practice and International Committee on Harmonization guidelines. The informed consent form contained all the essential elements of informed consent as stated in 21 CFR 50.25. An analysis of protocol deviations was included in this submission.

The final protocol was version 4.0, dated 20 November 2020. The informed consent was reviewed and approved by a central Institutional Review Board (IRB), (b) (4) that was used by all participating clinical sites. The final informed consent form was version 1.0, dated 4 June 2018. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC was given to the Applicant before study initiation.

The Bioresearch Monitoring Committee (BIMO) did not conduct investigations of the clinical sites included in V130_10 as part of STN 125408/351 due to limitations of BIMO inspection resources related to the Coronavirus Disease 2019 (COVID-19) pandemic. Of note, clinical site 84045 was inspected by BIMO in 2020 as part of the review for Fluad Quadrivalent under STN 125510/143.

Reviewer comment: *There were no unusual findings among the data for V130_10 that would warrant a request for clinical site inspection.*

3.3 Financial Disclosures

Covered clinical study: V130_10
Was a list of clinical investigators provided? ☒ Yes ☐ No (Request list from Applicant)
Total number of investigators identified: 47
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):

_____

Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant)

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

4.1 Chemistry, Manufacturing, and Controls

QIVc is a cell-based quadrivalent inactivated subunit vaccine that is prepared from virus propagated in Madin-Darby canine kidney (MDCK) cells, in contrast to the egg-based manufacturing process used for Afluria Quadrivalent.

4.2 Assay Validation

Data to support the validation of the MN assay using cell-based target viruses were submitted by the Applicant in September 2019. Complete validation reports for the MN assay using cell-based target viruses were accepted by the product review team for assessment of primary immunogenicity endpoints for strain A/H3N2 in December 2019. Please see Section 2.5 of this review for further details.

4.3 Nonclinical Pharmacology/Toxicology

This sBLA did not include new pharmacology or toxicology information.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Vaccination with inactivated influenza vaccines induces antibody responses against hemagglutinin and neuraminidase. Strain-specific neutralizing antibodies against hemagglutinin are the primary dirvers of protection against infection and clinical disease. Anti-hemagglutinin antibody responses are best measured using HAI assay. To date, HAI titers are considered the most reliable surrogate marker to predict clinical benefit. Specific HAI titers associated with protection against laboratory-confirmed influenza infection have yet to be identified in prospective studies. However, some studies suggest that HAI titers ranging from 1:32 to 1:40 are associated with protection from seasonal influenza infection in approximately 50% of subjects. Protection from illness is generally associated with higher HAI titers.

4.4.2 Human Pharmacodynamics (PD)

Not applicable.

4.4.3 Human Pharmacokinetics (PK)

Not applicable.

4.5 Statistical

The statistical reviewer has verified that the primary study endpoint analyses cited by the Applicant were supported by the submitted data.

4.6 Pharmacovigilance

The Applicant's current pharmacovigilance plan (PVP) is dated December 14, 2020. The Applicant is planning routine pharmacovigilance activities for continued assessment of QIVc, including surveilling for the Important Identified Risk of anaphylaxis and the following Important Potential Risks, which were included in the Risk Management Plan as plausible class effects: convulsions, Guillain-Barre syndrome, demyelination, vasculitis, and immune thrombocytopenic purpura. The pregnancy registry study for QIVc, V130_11OB has been completed and the results were submitted under STN 125408/(b) (4) and are currently under review.

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

5.1 Review Strategy

This sBLA was submitted electronically and included results from one study, V130_10, to support the immunogenicity and safety of QIVc in children 6 months through 3 years of age. The clinical, labeling, and financial disclosure information sections of the application were reviewed with detailed analyses of the study report, pertinent line listings, case report forms, and datasets.

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

The following sBLA amendments were reviewed:

- Amendment 0: Modules (M): M1.1, M1.2, M1.3, M1.4, M1.12, M1.13, M1.14, 1.16, M2.2, M2.5, M2.7, M5.3.1, M5.3.5
- Amendment 1, response to information request (IR) regarding immunogenicity assays: M1.11, M5.3.1
- Amendment 2, response to IR regarding validation of study data: M1.11, M5.3.5
- Amendment 3, proposed product labeling (clean and tracked changes), revised to reflect label change following approval for individuals 4 years of age and older: M1.14
- Amendment 4, response to IR regarding missingness of data from FAS to FAS Immunogenicity population, including sensitivity analyses: M1.11
- Amendment 5, response to IR for additional clinical documentation regarding subject ID V130-10-(b) (6) and presumptive diagnosis of adenovirus encephalitis: M1.11
- Amendment 6, response to IR for safety review of seizure events and clarification of solicited safety data collection procedures: M1.1, M1.2, M1.11
- Amendment 7, response to IR for revisions of the product label: M1.1, M1.2, M1.11, M1.14
- Amendment 8, response to IR for revisions of the product label: M1.1, M1.2, M1.11, M1.14

5.3 Table of Studies/Clinical Trials

Table 2. List of Clinical Studies

Study Number	Country	Description Relevant to U.S. Licensure	Population	Study Groups: #Exposed
Pivotal Study V130_10	United States	Phase 3 Immunogenicity Safety	Healthy subjects 6 months through 3 years (<4 years)	QIVc: 1597 QIV: 805

QIVc: Flucelvax Quadrivalent, QIV: Afluria Quadrivalent

5.4 Consultations

5.4.1 Advisory Committee Meeting

An Advisory Committee meeting was not convened during the review of this sBLA because CBER did not identify any review issues that warranted Advisory Committee input.

5.4.2 External Consults/Collaborations

No external consultations were obtained during the review of this sBLA.

5.5 Literature Reviewed

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13. McCullers, JA. Influenza Viruses. In Cherry, Harrison, Kaplan, Steinbach, Hotez. Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 8th ed.: Elsevier; 2018, 1470-1472.

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6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1 (V130_10)

NCT#04074928
A Phase 3, Randomized, Observer-Blind, Multicenter, Noninferiority Study to Evaluate Safety and Immunogenicity of a Cell-based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) and a United States-licensed Quadrivalent Influenza Virus Vaccine (QIV) in Health Subjects 6 Months Through 47 Months

6.1.1 Objectives

Primary Immunogenicity Objective
The primary immunogenicity objective was to demonstrate that vaccination with QIVc elicits an immune response that is non-inferior to that of a U.S.-licensed QIV containing the recommended strains for the season, in subjects 6 months through 47 months of age, as measured by HAI assay for A/H1N1, B/Yamagata, and B/Victoria strains and by MN assay for A/H3N2 strain, using cell-derived target viruses. The immunogenicity of study vaccines was evaluated at Day 1 and Day 29 for "previously vaccinated" subjects who received one vaccine dose and on Day 1 and Day 57 for "not previously vaccinated" subjects who received two vaccine doses.

Co-Primary Immunogenicity Endpoints

1. Serum HAI titer against A/H1N1, B/Yamagata, and B/Victoria vaccine strains at Day 29/57, using cell-derived target viruses:
    a. GMT by HAI assay.
    b. SCR defined as the percentage of subjects with either a prevaccination HAI titer <1:10 and a postvaccination HAI titer ≥1:40, or a prevaccination HAI titer ≥1:10 and a ≥4-fold increase in postvaccination HAI titer.

2. Serum MN titer against A/H3N2 vaccine strain at Day 29/57, using cell-derived target viruses:
    a. GMT by MN assay.
    b. SCR defined as the percentage of subjects with either a prevaccination MN titer <1:10 and a postvaccination MN titer ≥1:40, or a prevaccination MN titer ≥1:10 and a ≥4-fold increase in postvaccination MN titer.

Derived variables included the GMT ratio (QIV/QIVc) for each strain and the intergroup difference in the SCRs (QIV minus QIVc) for each strain. The noninferiority of QIVc compared with QIV was assessed for the following eight co-primary endpoints of GMT and SCR for each cell-derived target virus strain included in QIVc as follows:

- The GMT ratio for the A/H1N1 strain via HAI assay
- The GMT ratio for the A/H3N2 strain via MN assay
- The GMT ratio for the B/Yamagata strain via HAI assay
- The GMT for the B/Victoria strain via HAI assay
- The difference between the SCRs for the A/H1N1 strain via HAI assay
- The difference between the SCRs for the A/H3N2 strain via MN assay
- The difference between the SCRs for the B/Yamagata strain via HAI assay
- The difference between the SCRs for the B/Victoria strain via HAI assay

Secondary Immunogenicity Objectives

1. To describe the immunogenicity of QIVc and QIV by HAI assay for A/H1N1, B/Yamagata, and B/Victoria strains, and by MN assay for A/H3N2 strain, using egg-derived target viruses.

2. To describe the immunogenicity of QIVc and QIV by HAI assay for A/H1N1, B/Yamagata, and B/Victoria strains, and by MN assay for A/H3N2 strain, using cell-derived target viruses.

3. To describe the immunogenicity of QIVc and QIV by MN assay for A/H1N1, B/Yamagata, and B/Victoria strains, in a subset of subjects.

Secondary Safety Objective
To evaluate the safety and reactogenicity of QIVc and QIV.

Secondary Immunogenicity Endpoints

1. Humoral immune response in terms of HAI antibodies against A/H1N1, B/Yamagata, and B/Victoria strains using cell-derived and egg-derived target viruses:
    a. GMT by HAI assay at Days 1 and 29/57.

b. Geometric mean ratio (GMR), defined as the fold increase in serum HAI GMT postvaccination (Day 29/57) compared to prevaccination (Day 1).
c. Seropositivity rates (percentage of subjects with HAI titer ≥1:10) at Days 1 and 29/57.
d. Percentage of subjects with HAI titer ≥1:40 at Days 1 and 29/57.
e. SCR measured by HAI assay.

Derived variables:

f. The GMT ratio (QIV:QIVc) for each strain.
g. The intergroup difference in SCRs (QIV minus QIVc) for each strain.

2. Neutralizing antibody titers against A/H3N2 vaccine strains, using cell-derived and egg-derived target viruses
    a. GMT by MN assays at Days 1 and 29/57.
    b. GMR, defined as the fold increase in serum MN GMT postvaccination (Day 29/57) compared to prevaccination (Day 1).
    c. Seropositivity rates (percentages of subjects with MN titer ≥1:10 [the lower limit of quantification (LLOQ)]) at Days 1 and 29/57.
    d. SCR by MN assay.

3. Neutralizing antibody titers against A/H1N1, B/Yamagata, and B/Victoria vaccine strains, in a subset of subjects:
    a. GMT by MN assay at Days 1 and 29/57.
    b. GMR, defined as the fold increase in MN GMT postvaccination (Day 29/57) compared to prevaccination (Day 1).
    c. Seropositivity rates (percentages of subjects with MN titer >1:10 [LLOQ]) at Days 1 and 29/57.
    d. SCR by MN assay.

    Derived variables:

    e. The GMR (QIV:QIVc) for each strain.
    f. The intergroup difference in SCRs (QIV minus QIVc) for each strain.

Secondary Safety Endpoints

1. Percentage of subjects with solicited adverse events (AEs) within 7 days after each study vaccination.

2. Percentage of subjects with any unsolicited AEs from Day 1 to Day 29/57.

3. Percentage of subjects with any serious adverse events (SAEs), new onset chronic diseases (NOCDs), or AEs leading to withdrawal during the study period.

6.1.2 Design Overview

V130_10 was a randomized, observer-blinded, multicenter, non-inferiority study to evaluate the safety and immunogenicity of Flucelvax Quadrivalent (QIVc) in comparison to Afluria Quadrivalent (QIV) vaccine that is currently licensed in the United States for use in persons 6 months of age and older.

Reviewer comment: *This study was observer-blinded because the volume of each dose of QIVc was higher for children 6 months through 35 months of age compared to the volume of each dose of QIV. Therefore, designated and unblinded healthcare professionals were responsible for administering each dose of the study vaccine. These*

healthcare professionals were not involved in postvaccination assessments or other data collection. All subjects and study personnel were blinded to which vaccine was administered to each subject.

Subjects who met eligibility criteria were randomized in a 2:1 ratio to receive either QIVc or QIV. Stratification via Interactive Response Technology ensured a balanced distribution among the age groups, with the aim that at least 30% of subjects were 6 months through 23 months of age and at least 30% of subjects were 4 months through 47 months of age.

Subjects previously vaccinated against influenza received a single dose of vaccine on Day 1; subjects not previously vaccinated received a dose of vaccine on Day 1 and Day 29. Previously vaccinated subjects were evaluated in clinic on Day 1 and Day 29. A reminder phone call to complete a Subject Diary Card occurred on Day 3, and safety follow-up phone calls were performed on Day 91 and Day 181. Subjects not previously vaccinated were evaluated in clinic on Day 1, Day 29, and Day 57. Reminder phone calls to complete the Subject Diary Card occurred on Day 3 and Day 31, and safety follow-up phone calls were performed on Day 119 and Day 209. Study participation concluded after the Study Completion Call 180 days after the last vaccination.

6.1.3 Population

Inclusion Criteria

1. Children age 6 through 47 months on the day of informed consent.
2. Individuals whose parent(s)/legally authorized representative(s) had provided written informed consent.
3. In general good health per the investigator's judgment.

Exclusion Criteria

1. Acute (severe) febrile illness. See "Criteria for Delay of Vaccination" below for details.
2. History of any anaphylaxis, serious vaccine reactions or hypersensitivities to any component of the vaccine.
3. Contraindication to IM vaccination and/or blood draws.
4. History of Guillain-Barre syndrome or other demyelinating conditions such as encephalomyelitis or transverse myelitis.
5. Abnormal function of the immune system resulting from clinical conditions, including:
    a. Known or suspected congenital or acquired immunodeficiency.
    b. Systemic administration of corticosteroids at any dose for more than 14 days, within 90 days prior to informed consent. Topical, inhaled, and intranasal corticosteroids are permitted. Intermittent use (i.e., 1 dose per 30 days) of intraarticular corticosteroids is also permitted.
    c. Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to informed consent.
6. Received blood products including immunoglobulin.

Reviewer comment: *The subject eligibility criteria reflect the general population for which QIVc will be indicated.*

Criteria for Delay of Vaccination
Otherwise eligible subjects who developed fever (i.e., ≥38.0°C/≥100.4°F) within 3 days of vaccination, or who received antipyretic or analgesic medications within 24 hours of vaccination, warranted delay of vaccination until the above defined windows for delay had elapsed. Delay of vaccination under these circumstances was not considered a protocol deviation.

Criteria for Receipt of Second Study Vaccination
Prior to receipt of the second study vaccine, subjects were evaluated to confirm that they remained study eligible. If subjects met any of the original exclusion criteria or had experienced severe tolerability issues, they were not given the second dose of the study vaccine.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects received an intramuscular (IM) dose of QIVc or QIV into the anterolateral aspect of the thigh or into the deltoid muscle. Subjects not previously vaccinated against influenza received a second dose of QIVc or QIV on Day 29.

QIVc
Each subject randomized to QIVc received a 0.5 mL IM dose containing 60 µg of hemagglutinin (HA) antigen: 15µg HA of each of the two influenza type A strains, and 15µg HA each of the two influenza type B strains.

Table 3. QIVc Vaccine Composition

Names of Ingredients	Quantity per Dose[a] (0.5 mL/dose)	Function
Active Ingredients Hemagglutinin and neuraminidase antigens from the influenza virus strains recommended by the WHO/CBER/CHMP for the respective season A/Idaho/07/2018 (A/H1N1) A/Indiana/08/2018 (A/H3N2) B/Singapore/INFTT-16-0610/2016 (B/Yamagata) B/Iowa/06/2017 (B/Victoria)	15 µg HA (per strain)	Influenza vaccine
Other Ingredients		
Buffer M (PBS) (b) (4)		
(b) (4)		
Water for injection(s)	Up to 0.5 mL	Diluent

Abbreviations: CBER = Center for Biologics Evaluation and Research; CHMP = Committee for Medicinal Products for Human Use; DNA = deoxyribonucleic acid; HA = hemagglutinin; MDCK = Madin-Darby Canine Kidney; mg = milligram; mL = milliliter; µg = microgram; PBS = phosphate-buffered saline; QIVc = cell-based quadrivalent subunit influenza virus vaccine; WHO = World Health Organization.

[a] The quantities indicated in this table reflect the amount in a 0.5 mL dose.

Note: Each 0.5mL dose of Flucelvax Quadrivalent may contain residual amounts of β-propiolactone (<0.5 µg), cetyltrimethlyammonium bromide (≤18 µg), polysorbate 80 (≤1500 µg), MDCK cell protein (≤25.2 µg), protein other than HA (≤240 µg), MDCK cell DNA (≤10 ng), which are used in the manufacturing process. The 0.5 mL prefilled syringes contain no preservative or antibiotics.

Source: STN 125408 SN351, V130_10 Clinical Study Report, Table 9-1, p. 40

The product lot number was #261303 (expiration date: June 19, 2020).

QIV
The active comparator was QIV (Afluria Quadrivalent), an inactivated egg-based quadrivalent influence vaccine composed of antigens from two influenza A strains (A/H1N1 and A/H3N2) and 2 influenza B strains (B/Yamagata and B/Victoria). The age indication for QIV was extended to children 6 months of age and older in October 2018.

Each subject randomized to QIV received the vaccine per package insert instructions. Subjects 6 months through 35 months of age received a 0.25 mL IM dose containing 30 µg of HA antigen (7.5 µg of each influenza strain). Subjects 36 months through 47 months of age received a 0.5 mL IM dose containing 60 µg of HA antigen (15 µg of each influenza strain).

Reviewer comment: *For subjects 6 months through 35 months of age, the total HA antigen dose in QIV is half the amount of total HA antigen compared to QIVc. However, the difference in antigen dosing does not impact the interpretation of comparisons of immunogenicity between the treatment arms.*

Table 4. Afluria Quadrivalent Vaccine Composition

Names of Ingredients	Quantity per Dose[a] (0.5 mL/dose)	Function
Active Ingredients Hemagglutinin and neuraminidase antigens from the influenza virus strains recommended by the WHO/CBER/CHMP for the respective season A/Brisbane/02/2018 (IVR-190) (A/H1N1) A/Kansas/14/2017 (X-327) (A/H3N2) B/Phuket/3073/2013 (BVR-1B) (B/Yamagata) B/Maryland/15/2016 (B/Victoria)	15 µg HA (per strain)	Influenza vaccine
Other Ingredients		
Sodium chloride	4.1 mg	Maintains tonicity
Dibasic sodium phosphate	300 µg	Buffer
Monobasic sodium phosphate	80 µg	Buffer
Monobasic potassium phosphate	20 µg	Buffer
Potassium chloride	20 µg	Buffer
Calcium chloride	0.5 µg	Buffer
Water for injection(s)	Up to 0.5 mL	Solvent

Abbreviations: CBER = Center for Biologics Evaluation and Research; CHMP = Committee for Medicinal Products for Human Use; HA= hemagglutinin; mg = milligram; mL = milliliter; µg = microgram; ng = nanogram; ppm = parts per million; WHO = World Health Organization.

[a] The quantities indicated in this table reflect the amount in a 0.5 mL dose. Per the US Package Insert, a 0.25 mL dose is administered in children 6 through 35 months. This dose will contain half of these quantities.

Note: Each 0.5 mL dose of Afluria Quadrivalent may contain residual amounts of sodium taurodeoxycholate (≤10 ppm), ovalbumin (<1 µg), sucrose (<10 µg), neomycin sulfate (≤81.8 ng), polymyxin B (≤14 ng), beta-propiolactone (≤1.5 ng) and hydrocortisone (≤0.56 ng).

Source: STN 125408 SN351, V130_10 Clinical Study Report, Table 9-2, p. 41

6.1.5 Directions for Use

QIVc was provided in prefilled syringes, with an injectable volume of approximately 0.5 mL. The full volume contained in the prefilled syringe was administered. QIV was supplied in a 5 mL multi-dose vial containing twenty 0.25 mL doses or ten 0.5 mL doses and was administered as per the U.S. Prescribing Information.

For both QIVc and QIV, a 25 gauge, 25mm (1 inch) needle was recommended for vaccine administration. Subjects 6 months through 11 months of age received a single IM injection in the anterolateral region of the thigh. Subjects 12 months of age and older received a single IM injection in the deltoid region.

6.1.6 Sites and Centers

V130_10 was conducted at 47 investigational sites in the United States.

The principal investigator for this study was Brandon Essink, MD, CPI of Meridian Clinical Research, United States. There were also site-specific principal investigators for each study center.

6.1.7 Surveillance/Monitoring

Study oversight
V130_10 did not have a designated data monitoring committee (DMC); however, one SAE with a fatal outcome was reviewed by the independent DMC used for Study V130_14, another pediatric study that was conducted by the Applicant. The Applicant was responsible for oversight of the contract research organizations and (b) (4) was responsible for site monitoring activities.

Safety monitoring
Postvaccination safety monitoring for immediate AEs occurred for 30 minutes at the study site under medical supervision. Each subject's parent or legally authorized representative was instructed on measurements of solicited local and systemic AEs including body temperature, and on completion of the Subject Diary Card. Solicited AEs were collected for 7 days after each vaccination. All solicited local and systemic AEs were considered causally related to vaccination.

Reviewer comment: *The clinical study report tables describe the time period of collection of solicited adverse reactions outside of the immediate postvaccination period as "6h to 7 days." An IR was submitted to the Applicant to clarify whether this window included adverse reactions that occurred between 30 minutes and 6 hours postvaccination. In Amendment 6 to the sBLA, the Applicant clarified that caregivers were instructed to complete the diary card at the same time every day, preferably in the evening (i.e., approximately 6 hours postvaccination). Therefore, solicited adverse reactions that occurred at least 30 minutes postvaccination were collected in the diary card.*

The grading scale for all solicited local and systemic adverse events is provided below:

Table 5. Grading Scale for Local and Systemic Adverse Reactions

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)
Injection site tenderness (<24 months of age)	None	Minor reaction to touch	Cries or protests to touch	Cries when limb is moved, or if pain is spontaneous
Injection site tenderness (≥24 months of age)	None	No interference with daily activity	Interferes with daily activity	Prevents daily activity
Change of eating habits	None	Eating less than normal for 1-2 feeds or meals	Missed 1 or 2 feeds or meals	Missed ≥2 feeds or meals

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)
Sleepiness	None	Increased drowsiness	Sleeps through meals or feeds	Sleeps most of the time and is difficult to arouse
Vomiting	None	1-2 times in 24 hours	3-5 times in 24 hours	≥6 times in 24 hours or requires intravenous rehydration
Diarrhea	<2 loose stools in 24 hours	2-3 loose stools in 24 hours	4-5 loose stools in 24 hours	≥6 loose stools in 24 hours or requires intravenous rehydration
Irritability	None	Requires more cuddling, less playful than usual	More difficult to settle	Unable to console
Shivering	None	Present but not interfering with daily activity	Interferes with daily activity	Prevents daily activity
Temperature	<38ºC	≥38ºC to <39ºC	≥39ºC to <40ºC	≥40ºC

Source: Adapted from STN 125408/351, V130_10 Clinical Study Report, Table 3, p. 19

Injection site erythema, ecchymosis, and induration were graded based on the following linear measurements: “none” (0 mm), “any” (1 to <10 mm, 10 to 25 mm, 26 to 50 mm), and “severe” (>50 mm).

Unsolicited AEs were events that were spontaneously reported to the site by a subject or their legally authorized representative. All unsolicited AEs were collected during the treatment period (i.e., Day 1 to Day 29 for previously vaccinated subjects, Day 1 to Day 57 for subjects not previously vaccinated). The prespecified subsets of unsolicited AEs were serious adverse events (SAEs), which met the regulatory definition of seriousness as defined in 21 CFR 312.32, medically attended adverse events (MAAEs), defined as events which require hospitalization, emergency department visitation, or visitation to a healthcare provider’s office, new onset chronic diseases (NOCD), defined as a new diagnosis of a chronic medical condition that was not present or suspected in a subject prior to study enrollment, and AEs that led to study withdrawal. Unsolicited AEs were graded using the following criteria:

- Mild: transient with no limitation in normal daily activity.
- Moderate: some limitation in normal daily activity.
- Severe: unable to perform normal daily activity.

During the follow-up period (i.e., from Day 29 through Day 181 for previously vaccinated subjects, from Day 57 through Day 209 for subjects not previously vaccinated), serious adverse events (SAEs), NOCDs, MAAEs, and AEs leading to study withdrawal were collected.

6.1.8 Endpoints and Criteria for Study Success

Please see Section 6.1.1 of this review memo for study endpoints and criteria for study success.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The analysis of study data was based on the final Statistical Analysis Plan, version 3.0 (dated 13 May 2020).

Sample Size and Power Estimation
Assumed values for the power estimation calculation were based on immunogenicity experience with the Flucelvax Trivalent vaccine. The assumed GMT ratios for A/H1N1, A/H3N2 (using MN), and B strains, which were calculated using QIV/QIVc, were 1.49, 1.0, and 0.84, respectively. The standard deviation of log (titer) was 1.3 across all strains. The assumed QIVc seroconversion rates for A/H1N1, A/H3N2, and B strains were 81%, 85%, and 69%, respectively, and the expected difference between treatment arms (QIVc – QIV) was 7% for A/H1N1, 5% for A/H3N2, and 0% for the type B strains.

The Applicant estimated a requirement for approximately 1450 evaluable subjects who received QIVc and 725 subjects who received QIV for primary immunogenicity analyses, assuming a subject dropout rate of 10%. In addition, approximately 50 QIVc and 30 QIV recipients were planned to be allocated to assessment of cell-mediated immunity exploratory endpoints. The estimated power for the four GMT ratio endpoints was 94.9% and the estimated power for the four seroconversion endpoints was 99.4%. The overall power of the eight endpoints was 94.33%.

Analyses for Primary Endpoints
GMT ratios for each of the four strains of influenza were estimated with an adjusted analysis which was determined using a general linear model fitted to log10-transformed postvaccination HAI or MN titers as the outcome variable and the following terms for covariates: vaccine treatment, pre-vaccination HAI or MN titer, age stratum, sex, vaccination history (i.e., whether the subject was vaccinated against influenza in the past year), age-by-vaccine interaction, and study site. The estimated difference and the confidence limits were back-transformed to obtain an adjusted GMT ratio with 95% confidence limits.

Individual HAI titers below the detection limit (<10) were set to half of that limit (5). Individual MN titers below the lower limit of quantification (LLOQ) were set to half that limit (0.5*LLOQ).

Percentages of subjects who demonstrated seroconversion and subjects with titers ≥1:40 were summarized for each group using unadjusted estimates with two-sided 95% confidence intervals.

For immunogenicity data, imputation methods were not used.

Reviewer comment: *As described earlier in this review, evolutionary changes of influenza strain A/H3N2 appeared to result in the loss of capacity to agglutinate red blood cells, thereby limiting the sensitivity of the HAI assay. The Applicant submitted data to support the validation of a MN assay, and CBER concurred that the MN assay could be used to assess the two co-primary immunogenicity endpoints for A/H3N2.*

Assessment of A/H3N2 immunogenicity using the HAI assay was kept as an exploratory endpoint.

Success Criteria for the Primary Immunogenicity Endpoints
QIVc was to be considered noninferior to QIV if the following statistical criteria were met:

For A/H1N1, B/Yamagata, B/Victoria:

- The upper bound of the two-sided 95% confidence interval for the ratio of the HAI GMTs does not exceed 1.5. The HAI GMT ratios were calculated as the HAI GMT for QIV divided by the HAI GMT for QIVc.

- The upper bound of the two-sided 95% confidence interval for the difference between the HAI SCRs does not exceed 10%. The difference in HAI SCRs was calculated as the HAI SCR for QIV minus the HAI SCR for QIVc.

For A/H3N2 only:

- The upper bound of the two-sided 95% confidence interval for the ratio of the MN GMTs does not exceed 1.5. The MN GMT ratios were calculated as the MN GMT for QIV divided by the MN GMT for QIVc.

- The upper bound of the two-sided 95% confidence interval for the difference between the MN SCRs does not exceed 10%. The difference in MN SCRs was calculated as the MN SCR for QIV minus the MN SCR for QIVc.

Because all eight of these co-primary immunogenicity endpoints needed to be met to declare overall noninferiority, no adjustment for type I error for multiplicity was required.

Null Hypothesis
The null hypothesis would be met if either of the following occurred:

- The upper bound of the two-sided 95% confidence interval for the ratio of the GMTs exceeds 1.5 using HAI assay for strains A/H1N1, B/Yamagata, and B/Victoria or using MN assay for strain A/H3N2.

- The upper bound of the two-sided 95% confidence interval for the difference between the SCRs exceeds 10% using HAI assay for strains A/H1N1, B/Yamagata, and B/Victoria or using MN assay for strain A/H3N2.

Subgroup Analyses
Immunogenicity analyses were stratified by the following groups:
- Pre-vaccination HAI titer <1:10 vs ≥1:10
- Pre-vaccination MN titer < LLOQ vs ≥ LLOQ
- Influenza vaccination within the past 12 months
- Any previous influenza vaccination
- Age groups: “6 months through 23 months” and “24 months through 47 months”
- Center
- Sex
- Race
- Ethnicity

Safety analyses were stratified by the following groups:

- Influenza vaccination within the past 12 months
- Any previous influenza vaccination
- Age groups: "6 months through 23 months" and "24 months through 47 months"
- Sex
- Race
- Time interval as follows:
    - Day 1 to Day 29, Day 29 to Day 181 in previously vaccinated subjects
    - Day 1 to Day 57, Day 57 to Day 209 in subjects not previously vaccinated

Handling of Missing Data
Missing safety and immunogenicity data were considered "missing completely at random," and only complete case analyses were conducted. No imputation of data was used.

Stages of Analysis
Analyses were conducted in two phases. First, the final analyses of the primary and secondary immunogenicity endpoints was conducted on cleaned and locked data after all subjects completed all immunogenicity assessments (i.e., 28 days after the last vaccination). An analysis of all solicited adverse events and unsolicited adverse events that were reported during the treatment period was also conducted at this time. The second phase of analysis presented all clinical study data collected up to 180 days following the last vaccination, including safety data collected during the follow-up period.

Only personnel conducting statistical analyses had access to the individual treatment codes for the treatment period analyses. Personnel conducting the study and assessing follow-up adverse events were not unblinded until the data were cleaned and locked at the end of the study.

Summary of Changes in the Planned Analysis
The following changes were made to the statistical analysis plan prior to the database lock.

Version 1.0 to Version 2.0 (10 December 2019):

- To align with version 4.0 of the protocol, the statistical analysis plan was revised to include an explanation that the final analysis of the primary and secondary immunogenicity endpoints and the analysis of all solicited AEs and unsolicited AEs collected during the treatment period would be conducted once all subjects completed the treatment period of the protocol (end of treatment period).

Version 2.0 to Version 3.0 (13 May 2020):

- Duplicate tables of the primary and secondary immunogenicity analyses may be produced for the FAS Immunogenicity population if there were a >5% difference in the total number of subjects between the PPS and FAS Immunogenicity.
- Revision to exploratory immunogenicity objective number 1 to include measurement of CD8+ T-cell responses in addition to measurement of CD4+ T-cell responses to provide a more comprehensive evaluation of cell-mediated immune responses to the QIV vaccines.

- Revisions to the definitions of the safety analysis populations were made as follows:
    - The definition of the "Overall Safety Set" was changed to: "all subjects who are enrolled in the Solicited Safety Set and/or the Unsolicited Safety Set."
    - The "Safety Set" was removed as it was equivalent to the "Overall Safety Set."
- Revisions to the definition of the FAS Immunogenicity population by removal of the following parts of the definition:
    - "Did not experience a laboratory-confirmed influenza illness between Day 1, Day 29, and Day 57."
    - "Did not receive any prohibited medication during the study that is medically assessed to potentially impact immunogenicity results."
- Definition of the time window of postvaccination blood collection for exclusion from the PPS was changed to exclude all blood samples collected ≥49 days after the last vaccination.

- To align with the grading system used in V130_12, the grading of solicited local AEs was changed so that events were summarized only as none (0 mm), any, or severe (>50 mm).

Additionally, the study was planned to be conducted in approximately 2502 subjects, based on a sample size of 2418 subjects in the Immunogenicity Group plus 84 subjects in the CMI population. Due to lower than expected recruitment and enrollment during the projected 6 weeks allotted, efforts to increase enrollment were initiated; however, the enrollment rate continued to be lower than expected across the majority of sites. The decision was made to end enrollment after 10 more weeks of recruitment at which point a total of 2414 subjects (96.5% of the planned number of subjects) were enrolled in the study.

Reviewer comment: *The amendments of the statistical analysis plan did not significantly impact the conduct or analysis of V130_10.*

Impact of COVID-19 Pandemic on Study Conduct
The majority of subjects completed the study or were in the follow-up period at the time the COVID-19 pandemic began. Measurement of metrics potentially influenced by the COVID-19 pandemic were performed on 6 March 2020, 2 June 2020, 7 July 2020, 3 August 2020, and 3 September 2020. The 2 June 2020 and the 7 July 2020 reports showed 34 (19% noncompliance) and 16 (34% noncompliance) missed/out-of-window visits, respectively, all of which were considered related to the COVID-19 pandemic. The 3 August 2020 report showed 14 (28% noncompliance) missed/out-of-window monitoring visits, of which one was considered related to the COVID-19 pandemic. The 3 September 2020 report showed 6 (12% noncompliance) missed/out-of-window office monitoring visits, all of which were considered related to the COVID-19 pandemic.

During this window, there were no missed safety phone calls, out-of-window safety phone calls, early terminations, or SAEs considered related to COVID-19.

Reviewer comment: *The COVID-19 pandemic did not have significant impact on the results of this study.*

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 2414 subjects ages 6 months through 47 months were enrolled and randomized: 1605 to QIVc and 809 to QIV. Among these subjects, 2402 received at least one vaccination, and 12 were not vaccinated during the study.

2080 subjects (86.2%) completed the study; 334 subjects (13.8%) were discontinued from the study. The most common reason for discontinuation from the study was lost to follow-up (265 subjects; 11.1%).

Analysis Populations:

All Enrolled Set: All 2414 subjects who were enrolled and randomized.

Full Analysis Set (FAS): All 2402 subjects who received at least one vaccination during the study.

FAS Immunogenicity Group: 2322 subjects from the FAS who were enrolled for evaluation of primary and secondary immunogenicity endpoints. This excludes the 80 subjects enrolled in the Cell-Mediated Immunity Group.

Cell-Mediated Immunity (CMI) Group: 80 subjects 24 through 47 months of age from the FAS who were not enrolled in the Immunogenicity Group. These subjects were enrolled for exploratory evaluation of cell-mediated immunity.

Reviewer comment: *Subjects were enrolled in either the CMI Group or the FAS Immunogenicity Group, not both, in order to not exceed blood draw volume limits.*

Per Protocol Set (PPS): All subjects in the FAS Immunogenicity Group for whom there was no protocol deviation that was assessed as having the potential to impact the immunogenicity results. The PPS contained 1667 subjects. The PPS was used for primary and secondary immunogenicity analyses.

6.1.10.1.1 Demographics

The following table provides an overview of the demographic characteristics of subjects enrolled in V130_10.

Table 6. Demographics and Baseline Characteristics of the Full Analysis Set (FAS)

Demographic Characteristic	**QIVc (n=1597)**	**QIV (n=805)**
Mean Age in Months (SD)	28.1 (11.54)	28.2 (11.63)
Age Group:		
6 months through 23 months (%)	595 (37.3)	299 (37.1)
24 months through 47 months (%)	1002 (62.7)	506 (62.9)
Sex Ratio M:F (%)	803:794 (50.3:49.7)	406:399 (50.4:49.6)

Demographic Characteristic	**QIVc (n=1597)**	**QIV (n=805)**
Racial Origin (%):		
White	1039 (65.1)	539 (67)
Black or African American	455 (28.5)	209 (26)
Asian	13 (0.8)	8 (1.0)
Native Hawaiian or Other Pacific Islander	8 (0.5)	6 (0.7)
American Indian or Alaska Native	11 (0.7)	11 (1.4)
Other	71 (4.4)	32 (4.0)
Ethnic Origin (%):		
Hispanic	434 (27.2)	226 (28.1)
Not Hispanic or Latino	1160 (72.6)	575 (71.4)
Not Reported	3 (0.2)	1 (0.1)
Body Mass Index (kg/m^2)		
Mean (SD)	16.99 (2.47)	17.15 (3.0)
Median	16.73	16.75
Previous Influenza Vaccination (%):		
Previously Vaccinated	810 (50.7)	430 (53.4)
Not Previously Vaccinated	787 (49.3)	375 (46.6)

Source: Adapted from STN 125408/351, Clinical Study Report V130_10, Table 10-6, p. 87

Reviewer comments:

- *A greater proportion of subjects (approximately 63%) were in the older age cohort (i.e., 24 through 47 months) compared to the younger age cohort (i.e., 6 through 23 months; 37%). This difference in the number of subjects in each age cohort is balanced between the QIVc arm and the QIV arm. Please see the subgroup analyses for safety and immunogenicity results below for details regarding differences in study results between these age groups.*

- *The demographic and baseline characteristics were comparable between treatment groups. White and African American/Black subjects were representative of the United States population; however, Asian Americans were underrepresented relative to the United States population (0.9% enrolled versus 5.7% of the U.S. population according to the 2019 Census Bureau). Subjects of Hispanic ethnicity were appropriately represented by the study population.*

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Not applicable.

6.1.10.1.3 Subject Disposition

The following tables provides an overview of the subject disposition and vaccination in the study.

Table 7. Subject Disposition of the All Enrolled Set

	QIVc (n=1605)	QIV (n=809)	Total (n=2414)
Total subjects enrolled	1605 (100%)	809 (100%)	2414 (100%)
Total subjects vaccinated	1597 (99.5%)	805 (99.5%)	2402 (99.5%)
Completed Protocol	1370 (85.4%)	710 (87.8%)	2080 (86.2%)
Reason for Discontinuation:	-	-	-
Adverse event	1 (0.1%)	0	1 (<0.1%)
Death	2 (0.1%)	0	2 (0.1%)
Withdrawal of consent	36 (2.2%)	16 (2%)	52 (2.2%)
Lost to follow-up	191 (11.9%)	76 (9.4%)	267 (11.1%)
Protocol deviation	0	0	0
Other	5 (0.3%)	7 (0.9%)	12 (0.5%)

Source: Adapted from STN 125408/351, V130_10 Clinical Study Report, Table 14.1.1.2.

Reviewer comment: *The adverse event leading to withdrawal from the study was an SAE of seizures 17 days after QIVc considered unrelated to vaccination; this event is described in detail in Section 6.1.12.4 Nonfatal Serious Adverse Events. The fatal SAEs leading to study withdrawal included road traffic accident and adenoviral encephalopathy, both of which were considered unrelated to vaccination; these events are described in detail in Section 6.1.12.3 Deaths.*

Table 8. Vaccination Administration of the All Enrolled Set

	QIVc n (%)	QIV n (%)	Total n (%)
Vaccination 1 given:	-	-	-
n	1605	809	2414
Yes	1597 (99.5%)	805 (99.5%)	2402 (99.5%)
No	8 (0.5%)	4 (0.5%)	12 (0.5%)
Vaccination 2 given:	-	-	-
n	792	379	1171
Yes	715 (90.3%)	350 (92.3%)	1065 (90.9%)
No	77 (9.7%)	29 (7.7%)	106 (9.1%)

Source: Adapted from STN 125408/351, V130_10 Clinical Study Report, Table 14.1.1.8.

Reviewer comment: *Four subjects experienced adverse events leading to discontinuation of vaccination (i.e., the second dose of the vaccine was indicated but not provided). Three subjects from the QIVc group discontinued vaccination because of AEs: one subject experienced decreased appetite, one subject developed seizures, and one subject developed volvulus. One subject from the QIV group was diagnosed with a*

viral rash and subsequently discontinued vaccination. These adverse events leading to discontinuation of vaccination did not have a significant impact on immunogenicity analyses.

Protocol Deviations
Major protocol deviations were reported in 643 subjects: 439 (27.4%) in the QIVc group and 204 (25.2%) in the comparator group. The most common deviation across groups was "serological results not available," reported for 276 (17.2%) subjects in the QIVc group and 117 (14.5%) subjects in the comparator group. The second most frequently reported protocol deviation was "did not comply with the study vaccination schedule," reported for 66 (4.1%) subjects in the QIVc group and 29 (3.6%) subjects in the comparator group. The next most frequently reported protocol deviation was "did not comply with blood draw schedule," reported for 49 (3.1%) subjects in the QIVc group and 32 (4.0%) subjects in the comparator group. The protocol deviation, "subject did not provide any postvaccination solicited safety data" was reported for 33 (2.1%) subjects in the QIVc group and 21 (2.6%) subjects in the comparator group.

Reviewer comment: *There was a significant decrement in the number of subjects in the FAS Immunogenicity (1787 subjects) relative to the FAS (2402 subjects). The majority of protocol deviations were "serological results not available," which were related to inability to collect sufficient blood volumes from subjects to conduct immunogenicity analyses. Subjects 6 months through 23 months of age were disproportionately affected, as this age group made up 38.5% of the FAS but represented 48% of the missing subjects between the FAS and FAS Immunogenicity populations.*

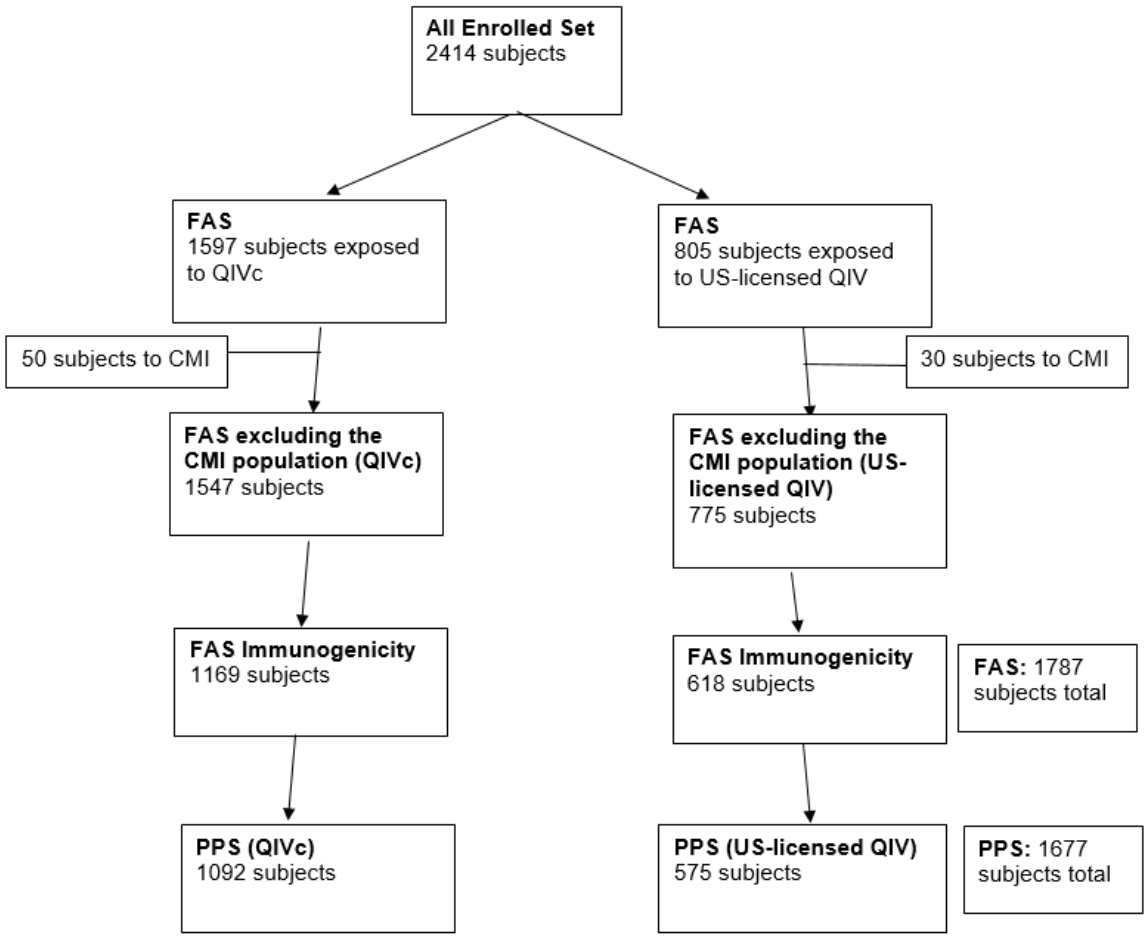
These missing data were evenly distributed between both arms of the study and were mostly not related to adverse events. Sensitivity analyses using the FAS demonstrated similar immunogenicity results as those conducted on the FAS Immunogenicity Group. Please see Section 6.1.11.1 for discussion of the sensitivity analyses submitted by the Applicant.

Table 9. Reasons for Exclusion from FAS Immunogenicity (excluding CMI Group)

	QIVc n(%)	**QIV n(%)**
FAS (excluding CMI)	**1547**	**775**
Early termination prior to V2 (if previously vaccinated) or V3 (if not previously vaccinated)	135 (8.7)	56 (7.2)
Serological results not available	260 (16.8)	109 (14.1)
FAS Immunogenicity	**1169 (75.6)**	**618 (79.7)**

Note: Subjects could be excluded from the FAS Immunogenicity Group for more than one reason. Therefore, the number of reasons for subject exclusion (e.g., early termination, serological results not available) is greater than the difference between the FAS and the FAS Immunogenicity groups.
Source: Adapted from STN 125408/351 clinical information amendment 4, Table 1, p. 2

Figure 1. Subject Disposition Flowchart



Source: Adapted from IND 019167 (b) (4), V130-10 Report Body, Figure 10.1, p. 82

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Primary Immunogenicity Objective

To demonstrate that vaccination with QIVc elicits an immune response that is non-inferior to the immune response elicited by a U.S.-licensed comparator influenza vaccine. Immunogenicity analyses will be conducted using cell-derived target influenza viruses.

Pre-determined Success Criteria for the Primary Immunogenicity Endpoints

Geometric Mean Titer Ratios (GMTRs): The upper bound of the two-sided 95% confidence interval for the ratio of the GMTRs does not exceed 1.5.

Seroconversion Rates (SCRs): The upper bound of the two-sided 95% confidence interval for the difference between the SCRs does not exceed 10%.

Primary immunogenicity assessments were performed using cell-derived target viruses.

The following table provides the data for the primary immunogenicity endpoints, as measured by GMT ratio and SCR, against A/H1N1, A/H3N2, B/Yamagata, and B/Victoria compared to the comparator vaccine. HAI assay was used for immunogenicity assessments of A/H1N1, B/Yamagata, and B/Victoria. The MN assay was used for immunogenicity assessments of A/H3N2.

Table 10. Immunogenicity of Flucelvax Quadrivalent (QIVc) Relative to Comparator (QIV) Using HAI Assay for Cell-Derived Target Virus Strains A/H1N1, B/Victoria, and B/Yamagata and MN assay for Cell-Derived Target Virus Strain A/H3N2 at Day 29 (Previously Vaccinated Subjects) or Day 57 (Vaccine-Naïve Subjects), Per-Protocol Set

Influenza Strain	QIVc (N_{HAI}=1092; N_{MN}=1078) GMT (95% CI)	QIV (N_{HAI}=575; N_{MN}=572) GMT (95% CI)	QIVc (N_{HAI}=1092; N_{MN}=1078) SCR (95% CI)	QIV (N_{HAI}=575; N_{MN}=572) SCR (95% CI)	Vaccine Group GMT Ratio	Vaccine Group SCR Difference
A/H1N1	78 (70.75, 86.03)	57.3 (50.76, 64.63)	58.24% (55.25, 61.19)	46.78% (42.64, 50.96)	0.73 (0.65, 0.84)	-11.46 (-16.45, -6.42)-
A/H3N2	23.1 (21.21, 25.12)	23.9 (21.57, 26.57)	27.64% (24.99, 30.42)	30.77% (27.01, 34.73)	1.04 (0.93, 1.16)	3.13 (-1.44, 7.81)-
B/Yamagata	35.6 (32.93, 38.58)	26 (23.54, 28.63)	46.52% (43.53, 49.53)	31.65% (27.87, 35.63)	0.73 (0.66, 0.81)	-14.87 (-19.61, -9.98)-
B/Victoria	22.4 (20.70, 24.19)	19.6 (17.81, 21.58)	30.31% (27.60, 33.13)	24.35% (20.89, 28.07)	0.88 (0.79, 0.97)	-5.96 (-10.33, -1.44)-

Source: Adapted from STN 125408/351 V130_10 Clinical Study Report, Table 11-1 and Table 11-2 (p. 92)

Reviewer comment: *The immunogenicity analyses met the prespecified success criteria for all eight immunogenicity endpoints.*

Given the decrement of subjects from the FAS to the FAS Immunogenicity, CBER sent an IR to the Applicant to verify the accuracy of their primary immunogenicity analyses given the unexpectedly high amount of missing immunogenicity data in the FAS Immunogenicity. The Applicant clarified that most of the missing data in the FAS Immunology and PPS were due to early termination prior to the second blood draw (9% and 7% for QIVc and QIV, respectively) or unavailable serology (17% and 14% for QIVc and QIV, respectively). The lack of available serology data was related to an inability to collect sufficient blood volume, predominately among infants and young toddlers.

Reviewer comment: *The proportions of subjects with missing serology data are balanced between both arms of the study. Further, the missing data are mostly related to limitations of blood volume collection from young subjects rather than vaccine-related adverse events which would result in discontinuation from the study. Thus, the missing serology data are unlikely to introduce bias that would interfere with this non-inferiority immunogenicity assessment.*

The Applicant conducted the following sensitivity analyses to account for the missing serology data from the FAS to the FAS Immunogenicity:

The Applicant used pattern-mixture models (PMM) with multiple imputations for analysis of the GMT outcome. The missing data among QIVc recipients were imputed from the available QIVc as well as the available QIV data. Imputed data were analyzed using the same model as the original PPS used to assess the primary immunogenicity endpoints. Results were reported as the median and maximum of the upper limit of the 95% confidence interval for each strain of influenza.

Table 11. Pattern-Mixture Models (PMM) of Imputed Upper Limits of 95% Confidence Intervals for GMT Ratios at Day 29/57

Strain and Assay	FAS Immuno GMT, 95% CI	PPS GMT, 95% CI	PMM upper confidence limit QIVc	PMM upper confidence limit QIV
A/H1N1 (HAI)	(0.62, 0.80)	(0.64, 0.84)	0.84	0.89
A/H3N2 (HAI)	(0.68, 0.87)	(0.69, 0.9)	0.89	0.97
A/H3N2 (MN)	(0.92, 1.15)	(0.93, 1.16)	1.19	1.2
B/Victoria (HAI)	(0.79, 0.96)	(0.79, 0.97)	1.02	1.02
B/Yamagata (MN)	(0.67, 0.82)	(0.66, 0.81)	0.85	0.89

Source: STN 125408/351, Amendment 4, Table 6, p. 9

The Applicant used a tipping point analysis for the SCR outcome. In brief, the tipping point analysis runs extreme imputation scenarios. In one scenario all missing SCR data is imputed as a seroconversion failure for QIVc and a seroconversion success for QIV. Another scenario imputes all missing seroconversion data as a success for QIVc and a failure for QIV. A conservative intent-to-treat analysis imputes missing data as "no success" for both study arms. The tipping point analysis of these scenarios verified that across all four influenza strains, either no or very few scenarios result in analyses that failed non-inferiority.

Reviewer comment: *The statistical review team concluded that the sensitivity analyses do not show evidence to contradict the Applicant's original conclusion of non-inferiority.*

6.1.11.2 Analyses of Secondary Endpoints

Secondary Immunogenicity Objective #1

The following table provides data to describe the immunogenicity of QIVc and QIV using egg-derived target viruses in the PPS population. These results are based on HAI titers for A/H1N1, B/Yamagata, and B/Victoria strains and MN titers for the A/H3N2 strain.

Table 12. Pre- and Postvaccination Immunogenicity Analyses of QIVc Compared to QIV Using HAI Assay for Egg-Derived Target Virus Strains A/H1N1, B/Yamagata, and B/Victoria and MN Assay for Egg-Derived Target Virus Strain A/H3N2 in the Per Protocol Set at Day 1 and Day 29/57

	QIVc n / % (95% CI)	QIV n / % (95% CI)
A/H1N1	**N=1092**	**N=575**
Day 1 HAI GMT	14.0 (12.54, 15.74)	13.9 (12.11, 16.04)
Day 29/57 HAI GMT	92.2 (83.62, 101.71)	82.9 (73.51, 93.58)
Day 29/57 HAI GMT Ratio	0.90 (0.790, 1.024)	0.90 (0.790, 1.024)

	QIVc n / % (95% CI)	QIV n / % (95% CI)
GMR HAI Titer	5.67 (5.117, 6.290)	5.11 (4.503, 5.809)
Day 1% GMT HAI Titer ≥1:10	52.47 (49.46, 55.47)	53.04 (48.87, 57.18)
Day 29/57% GMT HAI Titer ≥1:10	88.74 (86.71, 90.55)	92.34 (89.86, 94.39)
Day 1% HAI Titer ≥1:40	30.86 (28.13, 33.70)	30.96 (27.20, 34.91)
Day 29/57% HAI Titer ≥1:40	73.99 (71.28, 76.57)	74.78 (71.02, 78.28)
SCR (%) HAI Titer	58.52 (55.53, 61.46)	56.00 (51.83, 60.10)
SCR Difference	-2.52% (-7.526, 2.461)	-2.52% (-7.526, 2.461)
A/H3N2	**N=1079**	**N=572**
Day 1 MN GMT	12.9 (11.87, 13.96)	12.6 (11.42, 13.95)
Day 29/57 MN GMT	43.4 (39.58, 47.52)	44.7 (39.98, 50.08)
Day 29/57 MN GMT Ratio	1.03 (0.914, 1.165)	1.03 (0.914, 1.165)
GMR MN Titer	3.13 (2.856, 3.431)	3.22 (2.878, 3.608)
Day 1% GMT MN Titer ≥1:10	66.82 (63.92, 69.63)	66.78 (62.76, 70.64)
Day 29/57% GMT MN Titer ≥1:10	90.82 (88.94, 92.48)	87.94 (84.98, 90.49)
Day 1% MN Titer ≥1:40	19.93 (17.58, 22.44)	19.06 (15.92, 22.52)
Day 29/57% MN Titer ≥1:40	50.70 (47.67, 53.72)	46.68 (42.53, 50.86)
SCR (%) MN Titer	37.44 (34.55, 40.41)	39.34 (35.31, 43.47)
SCR Difference	1.89% (-3.006, 6.856)	1.89% (-3.006, 6.856)
B/Yamagata	**N=1092**	**N=575**
Day 1 HAI GMT	6.7 (6.33, 7.16)	6.7 (6.23, 7.26)
Day 29/57 HAI GMT	23.0 (21.21, 24.89)	24.7 (22.39, 27.26)
Day 29/57 HAI GMT Ratio	1.08 (0.968, 1.195)	1.08 (0.968, 1.195)
GMR HAI Titer	3.04 (2.808, 3.298)	3.27 (2.964, 3.615)
Day 1% GMT HAI Titer ≥1:10	28.75 (26.08, 31.54)	28.17 (24.53, 32.04)
Day 29/57% GMT HAI Titer ≥1:10	77.11 (74.50, 79.57)	79.13 (75.58, 82.38)
Day 1% HAI Titer ≥1:40	9.62 (7.93, 11.52)	8.87 (6.68, 11.50)
Day 29/57% HAI Titer ≥1:40	47.62 (44.62, 50.63)	45.57 (41.44, 49.74)
SCR (%) HAI Titer	38.64 (35.74, 41.61)	38.61 (34.61, 42.73)
SCR Difference	-0.04% (-4.912, 4.911)	-0.04% (-4.912, 4.911)
B/Victoria	**N=1092**	**N=575**
Day 1 HAI GMT	6.1 (5.77, 6.38)	6.0 (5.68, 6.43)
Day 29/57 HAI GMT	13.6 (12.58, 14.61)	14.8 (13.46, 16.19)
Day 29/57 HAI GMT Ratio	1.09 (0.986, 1.202)	1.09 (0.986, 1.202)
GMR HAI Titer	2.14 (1.987, 2.308)	2.33 (2.126, 2.558)
Day 1% GMT HAI Titer ≥1:10	17.03 (14.85, 19.40)	16.35 (13.42, 19.63)
Day 29/57% GMT HAI Titer ≥1:10	62.00 (59.04, 64.89)	68.17 (64.19, 71.97)
Day 1% HAI Titer ≥1:40	4.58 (3.42, 5.99)	3.65 (2.27, 5.53)
Day 29/57% HAI Titer ≥1:40	23.81 (21.31, 26.45)	25.04 (21.55, 28.79)
SCR (%) HAI Titer	19.69 (17.37, 22.17)	20.87 (17.62, 24.42)
SCR Difference	1.18% (-2.805, 5.353)	1.18% (-2.805, 5.353)

Source: Adapted from STN 125408/351, V130_10 Clinical Study Report, Table 11-3, p 100-101
Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; HAI = hemagglutination inhibition; MN = microneutralization; QIV = quadrivalent influenza vaccine; QIVc = cell-based quadrivalent subunit influenza virus vaccine; SCR = seroconversion rate

Reviewer comment: *Using egg-derived target viruses, the Day 29/57 GMT ratios or seroconversion rates were comparable between QIVc recipients and QIV recipients, consistent with the immunogenicity findings for the primary immunogenicity endpoints.*

Secondary Immunogenicity Objective #2
The following table provides data to describe the immunogenicity of QIVc and QIV by HAI assay for A/H1N1, B/Yamagata, and B/Victoria strains, and by MN assay for A/H3N2 strain, using cell-derived target viruses.

Table 13. Pre- and Postvaccination Immunogenicity Analyses Using GMT, GMT Ratio, Seroconversion Rate, and Seroconversion Rate Differences Using HAI Assay for Cell-Derived Target Virus Strains A/H1N1, B/Yamagata, and B/Victoria and MN Assay for Cell-Derived Target Virus Strain A/H3N2 in the PPS at Day 1 and Day 29/57

	QIVc n / % (95% CI)	QIV n / % (95% CI)
A/H1N1	**N=1092**	**N=575**
Day 1 HAI GMT	13.5 (12.01, 15.14)	12.8 (11.06, 14.72)
Day 29/57 HAI GMT	78.0 (70.75, 86.03)	57.3 (50.76, 64.63)
Day 29/57 HAI GMT Ratio	0.73 (0.645, 0.836)	0.73 (0.645, 0.836)
GMR HAI Titer	5.34 (4.834, 5.910)	3.97 (3.506, 4.493)
Day 1% GMT HAI Titer ≥1:10	46.52 (43.53, 49.53)	47.48 (43.33, 51.65)
Day 29/57% GMT HAI Titer ≥1:10	89.65 (87.69, 91.40)	88.87 (86.01, 91.32)
Day 1% HAI Titer ≥1:40	26.74 (24.13, 29.47)	24.35 (20.89, 28.07)
Day 29/57% HAI Titer ≥1:40	71.06 (68.27, 73.74)	61.57 (57.45, 65.56)
SCR (%) HAI Titer	58.24 (55.25, 61.19)	46.78 (42.64, 50.96)
SCR Difference	-11.46% (-16.447, -6.423)	-11.46% (-16.447, -6.423)
A/H3N2	**N=1078**	**N=572**
Day 1 MN GMT	10.3 (9.53, 11.15)	10.1 (9.15, 11.10)
Day 29/57 MN GMT	23.1 (21.21, 25.12)	23.9 (21.57, 26.57)
Day 29/57 MN GMT Ratio	1.04 (0.927, 1.160)	1.04 (0.927, 1.160)
GMR MN Titer	2.11 (1.940, 2.298)	2.19 (1.977, 2.436)
Day 1% GMT MN Titer ≥1:10	53.90 (50.87, 56.90)	51.22 (47.04, 55.39)
Day 29/57% GMT MN Titer ≥1:10	75.51 (72.83, 78.05)	73.08 (69.24, 76.67)
Day 1% MN Titer ≥1:40	15.68 (13.56, 17.99)	13.99 (11.25, 17.10)
Day 29/57% MN Titer ≥1:40	42.02 (39.05, 45.03)	41.08 (37.02, 45.24)
SCR (%) MN Titer	27.64 (24.99, 30.42)	30.77 (27.01, 34.73)
SCR Difference	3.13% (-1.443, 7.812)	3.13% (-1.443, 7.812)
B/Yamagata	**N=1092**	**N=575**
Day 1 HAI GMT	7.9 (7.38, 8.51)	7.7 (7.04, 8.39)
Day 29/57 HAI GMT	35.6 (32.93, 38.58)	26.0 (23.54, 28.63)
Day 29/57 HAI GMT Ratio	0.73 (0.656, 0.809)	0.73 (0.656, 0.809)
GMR HAI Titer	4.12 (3.792, 4.467)	3.03 (2.735, 3.348)
Day 1% GMT HAI Titer ≥1:10	39.56 (36.65, 42.53)	36.70 (32.75, 40.78)
Day 29/57% GMT HAI Titer ≥1:10	89.84 (87.89, 91.56)	84.70 (81.49, 87.54)

	QIVc n / % (95% CI)	QIV n / % (95% CI)
Day 1% HAI Titer ≥1:40	12.73 (10.81, 14.85)	10.96 (8.52, 13.80)
Day 29/57% HAI Titer ≥1:40	56.59 (53.59, 59.56)	41.91 (37.84, 46.07)
SCR (%) HAI Titer	46.52 (43.53, 49.53)	31.65 (27.87, 35.63)
SCR Difference	-14.87% (-19.610, -9.983)	-14.87% (-19.610, -9.983)
B/Victoria	**N=1092**	**N=575**
Day 1 HAI GMT	7.7 (7.21, 8.17)	7.8 (7.26, 8.48)
Day 29/57 HAI GMT	22.4 (20.70, 24.19)	19.6 (17.81, 21.58)
Day 29/57 HAI GMT Ratio	0.88 (0.791, 0.972)	0.88 (0.791, 0.972)
GMR HAI Titer	2.65 (2.450, 2.864)	2.31 (2.100, 2.548)
Day 1% GMT HAI Titer ≥1:10	37.82 (34.93, 40.77)	36.87 (32.92, 40.96)
Day 29/57% GMT HAI Titer ≥1:10	77.84 (75.26, 80.27)	74.78 (71.02, 78.28)
Day 1% HAI Titer ≥1:40	10.99 (9.20, 13.00)	10.61 (8.21, 13.42)
Day 29/57% HAI Titer ≥1:40	38.46 (35.56, 41.42)	34.43 (30.55, 38.48)
SCR (%) HAI Titer	30.31 (27.60, 33.13)	24.35 (20.89, 28.07)
SCR Difference	-5.96% (-10.327, -1.440)	-5.96% (-10.327, -1.440)

Source: Adapted from STN 125408/351, V130_10 Clinical Study Report, Table 11-4, p. 104-105
Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; HAI = hemagglutination inhibition; MN = microneutralization; QIV = quadrivalent influenza vaccine; QIVc = cell-based quadrivalent subunit influenza virus vaccine; SCR = seroconversion rate

Reviewer comment: *The secondary immunogenicity endpoints were comparable between the study treatment arms.*

Secondary Immunogenicity Objective #3
The following table provides data to describe the immunogenicity of QIVc and QIV using the MN assay for strains A/H1N1, B/Yamagata, and B/Victoria in a randomly selected subset of the PPS (nominally 20%). Cell-derived target viruses were used for these analyses.

Table 14. Immunogenicity Analyses Using Microneutralization Assay with Cell-Derived Target Viruses Strains A/H1N1, B/Yamagata, and B/Victoria in the PPS at Day 29/57

	QIVc n / % (95% CI)	QIV n / % (95% CI)
A/H1N1	**N=195**	**N=122**
Day 1 MN GMT	20.0 (14.58, 27.50)	21.8 (15.39, 30.81)
Day 29/57 MN GMT	137.3 (106.46, 177.12)	105.8 (80.14, 139.58)
Day 29/57 MN GMT Ratio	0.77 (0.558, 1.062)	0.77 (0.558, 1.062)
GMR MN Titer	5.74 (4.356, 7.573)	4.29 (3.174, 5.811)
Day 1% GMT MN Titer ≥1:10	74.36 (67.63, 80.33)	77.05 (68.57, 84.18)
Day 29/57% GMT MN Titer ≥1:10	97.44 (94.12, 99.16)	97.54 (92.98, 99.49)
Day 1% MN Titer ≥1:40	35.38 (28.69, 42.54)	39.34 (30.62, 48.59)
Day 29/57% MN Titer ≥1:40	84.10 (78.20, 88.94)	74.59 (65.91, 82.04)
SCR (%) MN Titer	62.56 (55.37, 69.37)	48.36 (39.22, 57.58)
SCR Difference	-14.20% (-25.185, -2.973)	-14.20% (-25.185, -2.973)

	QIVc n / % (95% CI)	QIV n / % (95% CI)
B/Yamagata	**N=195**	**N=122**
Day 1 MN GMT	17.2 (14.51, 20.36)	16.8 (13.97, 20.23)
Day 29/57 MN GMT	57.4 (47.41, 69.50)	51.7 (41.91, 63.70)
Day 29/57 MN GMT Ratio	0.90 (0.707, 1.147)	0.90 (0.707, 1.147)
GMR MN Titer	3.14 (2.561, 3.854)	2.86 (2.284, 3.572)
Day 1% GMT MN Titer ≥1:10	93.33 (88.87, 96.40)	91.80 (85.44, 96.00)
Day 29/57% GMT MN Titer ≥1:10	98.46 (95.57, 99.68)	99.18 (95.52, 99.98)
Day 1% MN Titer ≥1:40	21.54 (15.99, 27.98)	17.21 (10.98, 25.10)
Day 29/57% MN Titer ≥1:40	75.90 (69.27, 81.72)	64.75 (55.59, 73.18)
SCR (%) MN Titer	47.18 (40.01, 54.44)	40.16 (31.39, 49.42)
SCR Difference	-7.02% (-17.967, 4.259)	-7.02% (-17.967, 4.259)
B/Victoria	**N=195**	**N=122**
Day 1 MN GMT	11.5 (9.82, 13.52)	11.1 (9.33, 13.25)
Day 29/57 MN GMT	21.7 (18.45, 25.53)	18.5 (15.47, 22.06)
Day 29/57 MN GMT Ratio	0.85 (0.693, 1.046)	0.85 (0.693, 1.046)
GMR MN Titer	1.88 (1.583, 2.241)	1.63 (1.344, 1.966)
Day 1% GMT MN Titer ≥1:10	66.67 (59.58, 73.24)	63.93 (54.75, 72.43)
Day 29/57% GMT MN Titer ≥1:10	87.69 (82.24, 91.95)	86.07 (78.63, 91.67)
Day 1% MN Titer ≥1:40	10.26 (6.38, 15.40)	8.20 (4.00, 14.56)
Day 29/57% MN Titer ≥1:40	35.38 (28.69, 42.54)	33.61 (25.31, 42.72)
SCR (%) MN Titer	15.38 (10.63, 14.75)	14.75 (8.98, 22.31)
SCR Difference	-0.63% (-8.464, 7.979)	-0.63% (-8.464, 7.979)

Source: Adapted from STN 125408/351, V130_10 Clinical Study Report, Table 11-5, p. 112-113
Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; HAI = hemagglutination inhibition; MN = microneutralization; QIV = quadrivalent influenza vaccine; QIVc = cell-based quadrivalent subunit influenza virus vaccine; SCR = seroconversion rate

Reviewer comment: *The GMTs were higher in each group on Day 29/57 compared to Day 1. The GMT ratios or seroconversion rates for strains A/H1N1, B/Yamagata, or B/Victoria were comparable between the QIVc and QIV groups when immunogenicity analyses were performed using the MN assay for these strains.*

6.1.11.3 Subpopulation Analyses

Subgroup analyses were stratified by the following factors:

Age

The following tables describe the primary immunogenicity endpoints (GMT, GMT ratios, and SCR) by age group (6-23 months and 24-27 months).

Table 15. Immunogenicity Endpoints in Children 6-23 Months, Using Cell-Derived Target Viruses, Day 29 or Day 57[a], Per-Protocol Set

Strain	QIVc N_{HAI}=366; N_{MN}=360 GMT (95% CI)	QIV N_{HAI}=203; N_{MN}=201 GMT (95% CI)	QIVc N_{HAI}=366; N_{MN}=360 SCR (95% CI)	QIV N_{HAI}=203; N_{MN}=201 SCR (95% CI)	GMT Ratio (QIV/QIVc)	SCR Difference (QIV %-QIVc%)
A/H1N1 (HAI)	41.8 (35.2, 49.1)	35.0 (28.5, 42.9)	47.3 (42.1, 52.5)	36.9 (30.3, 44.0)	0.84 (0.67, 1.05)	-10.32 (-18.54, -1.82)
A/H3N2 (MN)	17.3 (15.3, 19.5)	15.3 (13.2, 17.8)	18.3 (14.5, 22.7)	16.9 (12.0, 22.8)	0.89 (0.75, 1.04)	-1.42 (-7.75, 5.44)
A/H3N2 (HAI)	188.2 (162.2, 218.5)	118.6 (98.7, 142.6)	70.5 (65.5, 75.1)	61.6 (54.5, 68.3)	0.63 (0.52, 0.77)	-8.92 (-17.13, -0.85)
B/Yamagata (HAI)	24.6 (21.7, 28.0)	18.2 (15.5, 21.3)	39.3 (34.3, 44.6)	22.7 (17.1, 29.0)	0.74 (0.62, 0.88)	-16.68 (-24.08, -8.81)
B/Victoria (HAI)	17.0 (15.0, 19.1)	15.3 (13.2, 17.7)	24.3 (20.0, 29.0)	16.7 (11.9, 22.6)	0.90 (0.77, 1.06)	-7.57 (-14.12, -0.52)

a. Day 29 for previously vaccinated subjects and Day 57 for vaccine-naïve subjects
Source: Adapted from STN 125408/351, V130_10, Table 14.2.3.2.1.1 and Table 14.2.4.1.3.1

Table 16. Immunogenicity Endpoints in Children 24-47 Months, Using Cell-Derived Target Viruses, Day 29 or Day 57[a], Per-Protocol Set

Strain	QIVc N_{HAI}=726; N_{MN}=718 GMT (95% CI)	QIV N_{HAI}=372; N_{MN}=371 GMT (95% CI)	QIVc N_{HAI}=726; N_{MN}=718 SCR (95% CI)	QIV N_{HAI}=372; N_{MN}=371 SCR (95% CI)	GMT Ratio (QIV/QIVc)	SCR Difference (QIV %-QIVc%)
A/H1N1 (HAI)	129.2 (115.5, 144.6)	84.4 (73.5, 97.0)	63.8 (60.2, 67.3)	52.2 (46.9, 57.3)	0.65 (0.56, 0.76)	-11.62 (-17.77, -5.46)
A/H3N2 (MN)	29.8 (26.8, 33.1)	36.2 (31.8, 41.3)	32.3 (28.9, 35.9)	38.3 (33.3, 43.4)	1.22 (1.06, 1.40)	5.96 (0.01, 12.02)
A/H3N2 (HAI)	376.9 (334.7, 424.4)	380.3(328.5, 440.1)	73.2 (69.8, 76.4)	66.1 (61.1, 70.9)	1.01 (0.86, 1.18)	-7.04 (-12.90, -1.33)
B/Yamagata (HAI)	48.6 (44.3, 53.3)	36.0 (32.1, 40.4)	50.1 (46.4, 53.8)	36.6 (31.7, 41.7)	0.74 (0.66, 0.84)	-13.58 (-19.58, -7.40)
B/Victoria (HAI)	28.3 (25.7, 31.0)	24.7 (22.0, 27.8)	33.3 (29.9, 36.9)	28.5 (24.0, 33.4)	0.88 (0.78, 0.99)	-4.84 (-10.45, 1.00)

a. Day 29 for previously vaccinated subjects and Day 57 for vaccine-naïve subjects
Source: Adapted from STN 125408/351, V130_10, Table 14.2.3.2.1.1 and Table 14.2.4.1.3.1

Reviewer comment: *Immune responses for each strain in each vaccine were evident in both age groups (i.e., 6 months through 23 months, 24 months through 47 months). Subjects in the younger age group had lower GMTs, seropositivity rates, and titers ≥1:40 at Day 29/57 compared to subjects in the older age group for each of the four strains; however, within each age group, the immunogenic responses were comparable between treatment arms.*

The distribution of subjects from the younger age group is equivalent between arms of the study, and the immunogenicity results for QIVc were non-inferior to QIV among the PPS. Differences in overall immunogenicity between age groups is expected, and these differences do not introduce bias to the interpretation of the primary immunogenicity endpoints. These results support non-inferiority of QIVc for all strains for both age groups in this study.

Only the cell-derived results are shown in the tables above; however, these analyses were conducted using both cell-derived and egg-derived target viruses. Independent of the target virus used, no within age strata differences in response rates were observed..

Prevaccination Titer
The following tables provide the GMT and SCR data by prevaccination titer (<1:10 and >1:10).

Table 17. Immunogenicity Endpoints in Subjects with Prevaccination Titers <1:10, Using Cell-Derived Target Viruses, Day 29 or Day 57[a], Per-Protocol Set

Strain	QIVc N_{HAI}=584; N_{MN}=497 GMT (95% CI)	QIV N_{HAI}=302; N_{MN}=279 GMT (95% CI)	QIVc N_{HAI}=584; N_{MN}=497 SCR (95% CI)	QIV N_{HAI}=302; N_{MN}=279 SCR (95% CI)	SCR Difference (QIV %-QIVc%)
A/H1N1 (HAI)	34.1 (29.9, 38.8)	22.5 (19.1, 26.6)	54.5 (50.3, 58.6)	39.7 (34.2, 45.5)	0.84 (0.67, 1.05)
A/H3N2 (MN)	9.5 (8.7, 10.5)	8.8 (7.9, 9.9)	11.9 (9.2, 15.0)	9.7 (6.5, 13.8)	-2.2 (-6.5, 2.6)
A/H3N2 (HAI)	61.2 (51.0, 73.5)	39.6, (31.8, 49.3)	68.1 (62.0, 73.7)	64.0 (55.3, 72.0)	-4.1 (-14.1, 5.5)
B/Yamagata (HAI)	23.9 (21.6, 26.4)	17.1 (15.1, 19.3)	42.4 (38.6, 46.3)	25.8 (21.4, 30.6)	-16.6 (-22.3, -10.6)
B/Victoria (HAI)	14.1 (12.9, 15.4)	12.3 (10.9, 13.8)	20.0 (17.1, 23.2)	15.2 (11.6, 19.3)	-4.9 (-9.5, 0.1)

a. Day 29 for previously vaccinated subjects and Day 57 for vaccine-naïve subjects
Source: Adapted from STN 125408/351, V130_10, Table 14.2.3.1.1.2 and 14.2.3.2.1.2

Table 18. Immunogenicity Endpoints in Subjects with Prevaccination Titers >1:10, Using Cell-Derived Target Viruses, Day 29 or Day 57[a], Per-Protocol Set

Strain	QIVc N_{HAI}=508; N_{MN}=581 GMT (95% CI)	QIV N_{HAI}=273; N_{MN}=293 GMT (95% CI)	QIVc N_{HAI}=508; N_{MN}=581 SCR (95% CI)	QIV N_{HAI}=273; N_{MN}=293 SCR (95% CI)	SCR Difference (QIV %-QIVc%)
A/H1N1 (HAI)	231.1 (197.7, 270.0)	170.7 (142.2, 204.8)	62.6 (58.2, 66.8)	54.6 (48.5, 60.6)	-8.0 (-15.3, -0.8)
A/H3N2 (MN)	51.9 (45.4, 59.4)	68.0 (57.8, 80.1)	41.1 (37.1, 45.3)	50.9 (45.0, 56.7)	9.7 (2.7, 16.6)
A/H3N2 (HAI)	449.9 (396.92, 510.0)	408.5 (351.4, 474.9)	73.6 (70.4, 76.6)	64.7 (60.0, 69.1)	-8.9 (-14.3, -3.6)
B/Yamagata (HAI)	67.5 (58.7, 77.6)	54.5 (46.1, 64.4)	52.8 (48.0, 57.6)	41.7 (35.0, 48.7)	-11.1 (-19.1, -2.8)
B/Victoria (HAI)	49.0 (42.2, 56.9)	43.0 (36.2, 51.1)	47.2 (42.3, 52.1)	40.1 (33.4, 47.0)	0.90 (0.77, 1.06)

a. Day 29 for previously vaccinated subjects and Day 57 for vaccine-naïve subjects
Source: Adapted from STN 125408/351, V130_10, Table 14.2.3.1.1.2 and 14.2.3.2.1.2

Reviewer comment: *For each strain, the GMT responses measured by HAI assay were higher among QIVc recipients than QIV recipients. This may be attributed to the higher dose of hemagglutinin antigen in QIVc, and is less likely attributed to the use of cell-based target viruses in the assays, as similar results were observed when using cell-derived target viruses and egg-derived target viruses. Subjects with baseline titers ≥1:10 were noted to have overall higher Day 29/57 titers compared to subjects with baseline titers <1:10; however, these differences were balanced between treatment arms. There is no evidence to contradict noninferiority of QIVc when stratifying immunogenicity assessments by prevaccination titer.*

Influenza Vaccination History
Immune responses to vaccine were evident in previously vaccinated and vaccine-naïve subjects who received QIVc or QIV. Subjects previously vaccinated against influenza had higher titers at Day 29/57 compared to vaccine-naïve subjects.

Vaccine-naïve subjects who received QIVc had slightly lower Day 29/57 GMT responses and SCRs against strain B/Victoria than vaccine-naïve subjects who received QIVc; however, these values still met the noninferiority criteria used for the primary immunogenicity endpoints. The GMT responses and SCRs for all other strains were higher among QIVc recipients compared to QIV recipients in vaccine-naïve subjects. GMT responses and SCRs for all strains were higher among QIVc recipients compared to QIV recipients in the subgroup previously vaccinated against influenza.

Reviewer comment: *Immunogenicity results for the influenza vaccination history subgroup analysis were largely similar to the immunogenicity results for the prevaccination titer subgroup analysis, and thus the immunogenicity results are not presented in this review.*

Sex
The following tables provide the GMT and SCR data by sex (male and female).

Table 19. Immunogenicity Endpoints in Male Subjects, Using Cell-Derived Target Viruses, Day 29 or Day 57[a], Per-Protocol Set

Strain	QIVc N_{HAI}=555; N_{MN}=545 GMT (95% CI)	QIV N_{HAI}=286; N_{MN}=283 GMT (95% CI)	QIVc N_{HAI}=555; N_{MN}=545 SCR (95% CI)	QIV N_{HAI}=286; N_{MN}=283 SCR (95% CI)	SCR Difference (QIV %-QIVc%)
A/H1N1 (HAI)	74.5 (65.2, 85.1)	53.2 (45.1, 62.7)	56.2 (52.0, 60.4)	47.9 (42.0, 53.9)	-8.3% (-15.4, -1.2)
A/H3N2 (MN)	21.3 (19.0, 23.9)	22.8 (19.7, 26.3)	27.2% (23.5, 31.1)	29.3% (24.1, 35.0)	2.2% (-4.2, 8.8)
A/H3N2 (HAI)	281.8 (246.0, 322.7)	225.5 (190.8, 266.5)	72.9% (69.0, 76.5)	63.3% (57.4, 68.9)	-9.6% (-16.4, -3.0)
B/Yamagata (HAI)	35.0 (31.5, 39.0)	25.7 (22.5, 29.3)	46.7% (42.5, 50.9)	29.7% (24.5, 35.4)	-17.0% (-23.5, -10.1)
B/Victoria (HAI)	21.4 (19.3, 23.7)	18.9 (16.7, 22.6)	29.7% (26.0, 33.7)	23.4% (18.6, 28.8)	-6.3% (-12.4, 0.1)

a. Day 29 for previously vaccinated subjects and Day 57 for vaccine-naïve subjects
Source: Adapted from STN 125408/351, V130_10, Table 14.2.3.1.1.4, and Table 14.2.3.2.1.4

Table 20. Immunogenicity Endpoints in Female Subjects, Using Cell-Derived Target Viruses, Day 29 or Day 57[a], Per-Protocol Set

Strain	QIVc N_{HAI}=537; N_{MN}=533 GMT (95% CI)	QIV N_{HAI}=289; N_{MN}=289 GMT (95% CI)	QIVc N_{HAI}=537; N_{MN}=533 SCR (95% CI)	QIV N_{HAI}=289; N_{MN}=289 SCR (95% CI)	SCR Difference (QIV %-QIVc%)
A/H1N1 (HAI)	80.6 (70.0, 93.1)	56.1 (47.1, 66.9)	60.3% (56.1, 64.5)	45.7% (39.8, 51.6)	-14.7% (-21.7, -7.5)
A/H3N2 (MN)	24.3 (21.5, 27.6)	27.5 (23.6, 32.0)	28.1% (24.4, 32.2)	32.2% (26.8, 37.9)	4.0% (-2.5, 10.7)
A/H3N2 (HAI)	275.8 (239.8, 317.3)	256.6 (216.5, 304.1)	71.6% (67.6, 75.4)	65.7% (60.0, 71.2)	-5.9% (-12.6, 0.7)
B/Yamagata (HAI)	36.0 (32.0, 40.5)	26.7 (23.2, 30.8)	46.4% (42.1, 50.7)	33.6% (28.1, 39.3)	-12.8% (-19.6, -5.8)
B/Victoria (HAI)	23.5 (20.9, 26.5)	20.7 (17.9, 23.9)	30.9% (27.0, 35.0)	25.3% (20.4, 30.7)	-5.7% (-11.9, 0.9)

a. Day 29 for previously vaccinated subjects and Day 57 for vaccine-naïve subjects
Source: Adapted from STN 125408/351, V130_10, Table 14.2.2.2.1.4, Table 14.2.3.1.1.4, and Table 14.2.3.2.1.4

Reviewer comment*: As described previously, QIVc recipients had numerically higher GMT responses and seroconversion rates for all strains measured by HAI assay compared to QIV recipients. This difference may be attributed to the higher antigen dose of QIVc or because of the cell-based manufacturing process for QIVc. There were no notable differences in vaccine responses to QIVc and QIV between male and female subjects. There is no evidence to contradict the noninferiority of QIVc in this subgroup analysis.*

Race
The following tables provide the GMT and SCR data by race.

Table 21. Immunogenicity Endpoints in Subjects of White Race, Using Cell-Derived Target Viruses, Day 29 or Day 57[a], Per-Protocol Set

Strain	QIVc N_{HAI}=726; N_{MN}=719 GMT (95% CI)	QIV N_{HAI}=289; N_{MN}=385 GMT (95% CI)	QIVc N_{HAI}=726; N_{MN}=719 SCR (95% CI)	QIV N_{HAI}=388; N_{MN}=385 SCR (95% CI)	SCR Difference (QIV %-QIVc%)
A/H1N1 (HAI)	66.8 (58.5, 76.3)	47.9 (40.9, 56.2)	58.0% (54.4, 61.6)	44.9% (39.8, 50.0)	-13.1 (-19.1, -7.0)
A/H3N2 (MN)	19.5 (17.4, 21.8)	20.5 (18.0, 23.5)	24.8% (21.6, 28.0)	26.8% (22.4, 31.5)	2.0 (-3.3, 7.5)
A/H3N2 (HAI)	220.0 (192.7, 249.9)	194.4 (166.3, 227.2)	70.2% (66.7, 73.5)	63.7% (58.7, 68.5)	-6.5 (-12.4, -0.7)
B/Yamagata (HAI)	32.2 (29.0, 35.8)	23.7 (20.9, 26.9)	43.7% (40.0, 47.4)	29.6% (25.14, 34.5)	-14.0 (-19.7, -8.1)
B/Victoria (HAI)	22.2 (20.1, 26.1)	17.9 (15.8, 20.2)	29.1% (25.8, 32.5)	19.6% (15.8, 23.9)	-9.5 (-14.5, -4.2)

a. Day 29 for previously vaccinated subjects and Day 57 for vaccine-naïve subjects
Source: Adapted from STN 125408/351, V130_10, Table 14.2.3.1.1.5 and Table 14.2.2.2.1.5

Table 22. Immunogenicity Endpoints in Black or African American Subjects, Using Cell-Derived Target Viruses, Day 29 or Day 57[a], Per-Protocol Set

Strain	QIVc N_{HAI}=296; N_{MN}=291 GMT (95% CI)	QIV N_{HAI}=149;N_{MN}=149 GMT (95% CI)	QIVc N_{HAI}=296; N_{MN}=291 SCR (95% CI)	QIV N_{HAI}=149;N_{MN}=149 SCR (95% CI)	SCR Difference (QIV %-QIVc%)
A/H1N1 (HAI)	109.5 (87.8, 136.58)	74.4 (57.2, 96.8)	59.1% (53.3, 64.8)	51.7% (43.4, 59.9)	-7.4 (-17.2, 2.3)
A/H3N2 (MN)	34.2 (28.2, 41.6)	40.2 (31.9, 50.7)	34.4% (28.9, 40.1)	40.3% (32.3, 48.6)	5.9 (-3.5, 15.5)
A/H3N2 (HAI)	503.6 (403.7, 628.1)	404.3 (311.9, 524.12)	76.6% (71.4, 81.3)	64.4% (56.2, 72.1)	-12.2 (-21.4, -3.3)
B/Yamagata (HAI)	40.8 (34.2, 48.6)	30.7 (25.0, 37.8)	51.7% (45.8, 57.5)	36.9% (29.2, 45.2)	-14.8 (-24.1, -5.0)
B/Victoria (HAI)	27.1 (22.8, 32.3)	26.9 (21.8, 33.1)	34.8% (29.4, 40.5)	33.6% (26.0, 41.7)	-1.2 (-10.3, 8.3)

a. Day 29 for previously vaccinated subjects and Day 57 for vaccine-naïve subjects
Source: Adapted from STN 125408/351, V130_10 Clinical Study Report, Table 14.2.2.1.1.5 and Table 14.2.2.2.1.5

Table 23. Immunogenicity Endpoints in Asian Subjects, Using Cell-Derived Target Viruses, Day 29 or Day 57[a], Per-Protocol Set

Strain	QIVc $N_{HAI}=8$; $N_{MN}=7$ GMT (95% CI)	QIV $N_{HAI}=7$; $N_{MN}=7$ GMT (95% CI)	QIVc $N_{HAI}=8$; $N_{MN}=7$ SCR (95% CI)	QIV $N_{HAI}=7$; $N_{MN}=7$ SCR (95% CI)	SCR Difference (QIV %-QIVc%)
A/H1N1 (HAI)	76.6 (21.1, 278.4)	56.6 (14.2, 224.7)	62.5% (24.5, 91.5)	57.1% (18.4, 90.1)	-5.4% (-50.5, 41.4)
A/H3N2 (MN)	9.1 (3.9, 20.9)	12.2 (5.3, 28.2)	14.3% (0.4, 57.9)	28.6% (3.7, 71.0)	14.3% (-32.2, 55.9)
A/H3N2 (HAI)	113.1 (44.9, 285.4)	118.9 (44.2, 319.7)	87.5% (47.4, 99.7)	57.1% (18.4, 90.1)	-30.4% (-67.9, 16.7)
B/Yamagata (HAI)	59.1 (26.9, 129.6)	23.2 (10.0, 53.8)	62.5% (24.5, 91.5)	42.9% (9.9, 81.6)	-19.6% (-61.2, 30.2)
B/Victoria (HAI)	18.3 (6.8, 49.8)	22.1 (7.6, 64.2)	12.5% (0.3, 52.3)	14.3% (0.4, 57.9)	1.8% (38.2, 43.6)

Unadjusted GMT values were used for immunogenicity data using MN assay, as the adjusted GMT values could not be estimated for the Asian subpopulation.
a. Day 29 for previously vaccinated subjects and Day 57 for vaccine-naïve subjects
Source: Adapted from STN 125408/351, V130_10 Clinical Study Report, Table 14.2.2.1.1.5 and Table 14.2.2.2.1.5

Table 24. Immunogenicity Endpoints in Native Hawaiian or Other Pacific Islanders, Using Cell-Derived Target Viruses, Day 29 or Day 57[a], Per-Protocol Set

Strain	QIVc $N_{HAI}=7$; $N_{MN}=7$ GMT (95% CI)	QIV $N_{HAI}=3$; $N_{MN}=3$ GMT (95% CI)	QIVc $N_{HAI}=7$; $N_{MN}=7$ SCR (95% CI)	QIV $N_{HAI}=3$; $N_{MN}=3$ SCR (95% CI)	SCR Difference (QIV %-QIVc%)
A/H1N1 (HAI)	23.8 (0.0, 1979598)	345.5 (0.0, 7618853)	71.4% (29.0, 96.3)	66.7% (9.43, 99.2)	-4.8% (-62.1, 47.5)
A/H3N2 (MN)	39.7 (0.36, 4376.9)	29.2 (0.9, 932.4)	14.3% (0.4, 57.9)	28.6% (3.7, 71.0)	14.3% (-32.2, 55.9)
A/H3N2 (HAI)	793.0 (0.4, 1689694)	867.3 (1.6, 467623.4)	100% (59.0, 100.0)	100% (29.2, 100.0)	0%
B/Yamagata (HAI)	75.1 (0.5, 10528.5)	51.3 (0.63, 4144.4)	85.7% (42.1, 99.6)	66.7% (9.43, 99.2)	-19.1% (-71.8, 33.2)
B/Victoria (HAI)	59.6 (0.0, 1216108)	212.2 (0.0, 1796250)	28.6% (3.7, 71.0)	100% (29.2, 100.0)	71.4% (0.1, 92.3)

Unadjusted GMT values were used for immunogenicity data using MN assay, as the adjusted GMT values could not be estimated for the Asian subpopulation.
a. Day 29 for previously vaccinated subjects and Day 57 for vaccine-naïve subjects
Source: Adapted from STN 125408/351, V130_10 Clinical Study Report, Table 14.2.3.1.1.5 and Table 14.2.3.2.1.5

Table 25. Immunogenicity Endpoints in American Indian or Alaska Native Subjects, Using Cell-Derived Target Viruses, Day 29 or Day 57[a], Per-Protocol Set

Strain	QIVc N_{HAI}=6; N_{MN}=6 GMT (95% CI)	QIV N_{HAI}=4; N_{MN}=4 GMT (95% CI)	QIVc N_{HAI}=6; N_{MN}=6 SCR (95% CI)	QIV N_{HAI}=4; N_{MN}=4 SCR (95% CI)	SCR Difference (QIV %-QIVc%)
A/H1N1 (HAI)	359.3 (0.0, $2.1X10^9$)	290.8 (0.0, $2.0X10^9$)	33.3% (4.3, 77.7)	50% (6.8, 93.2)	16.7% (-41.7, 66.7)
A/H3N2 (MN)	74.0 (0.0, $3.8X10^9$)	11.0 (0.0, 99723586)	16.7% (0.4, 64.1)	25.0% (0.6, 80.6)	8.3% (-42.8, 61.1)
A/H3N2 (HAI)	137.3 (0.0, 17060705)	48.5 (0.0, 150125.2)	66.7% (22.3, 95.7)	75% (19.4, 99.4)	8.3% (-49.7, 57.5)
B/Yamagata (HAI)	46.1 (0.0, $1.6X10^{10}$)	14.6 (0.0, $5.3X10^9$)	50.0% (11.8, 88.2)	25.0% (0.6, 80.6)	-25.5 (70.0, 37.1)
B/Victoria (HAI)	13.7 (0.0, $6.5X10^9$)	24.1 (0.0, 783327.7)	33.3% (4.3, 77.7)	25.0% (0.6, 80.6)	-8.3% (-57.5, 49.7)

Unadjusted GMT values were used for immunogenicity data using MN assay, as the adjusted GMT values could not be estimated for the Asian subpopulation.
a. Day 29 for previously vaccinated subjects and Day 57 for vaccine-naïve subjects
Source: Adapted from STN 125408/351, V130_10, Table 14.2.3.1.1.5 and Table 14.2.3.2.1.5.

Reviewer comment: *Compared to White subjects, Black or African American subjects have higher GMT responses against all four strains following vaccination with QIVc or QIV. There were no notable differences in seroresponse between White subjects and Black or African American subjects following administration of QIVc or QIV; however, the White subgroup had higher SCRs for the B/Yamagata strain after receiving QIVc compared to QIV. Similarly, the Black or African American subgroup had higher SCRs against the B/Yamagata strain following vaccination with QIVc compared to QIV.*

Subgroup analyses using egg-derived target viruses showed no notable differences in immunogenicity between White and Black or African American subjects.

The Asian subgroup appeared to have higher SCRs using HAI assay for strains A/H3N2 and B/Yamagata following vaccination with QIVc compared to the White, Black or African American, and American Indian or Alaska Native subgroups. However, interpretation of this finding is confounded by the small number of Asian subjects (i.e., 8 QIVc recipients and 7 QIV recipients). Similarly, the Native Hawaiian or Other Pacific Islander subgroup appeared to have increased SCRs against B/Yamagata following vaccination with QIVc compared to the other racial subgroups but is represented by a very small number of subjects (i.e., 7 QIVc recipients and 3 QIV recipients) which limits the interpretation of these results.

Although the populations of Asian, Native Hawaiian or Other Pacific Islander, and American Indian or Alaska Native subgroups were too small to draw a meaningful comparison, there is no evidence to contradict the non-inferiority of QIVc to QIV for any racial group.

6.1.11.4 Dropouts and/or Discontinuations

Please see Section 6.1.11.1 (Analyses of Primary Endpoints) for discussion regarding decrement of sample size from the FAS to the FAS Immunogenicity populations related to missing serology data. The missing serology data were primarily attributed to phlebotomy limitations in young children. In response to an IR, the Applicant provided sensitivity analyses demonstrating that the loss of immunogenicity data was balanced between QIVc and comparator arms, the missing data were not related to treatment-related effects, and the missing immunogenicity data likely did not introduce bias to the study.

As described in Section 6.1.10 (Study Population and Disposition), a total of 334 subjects discontinued from the study and a total of 106 subjects did not receive the second study vaccination as planned.

Reviewer comment*: The proportions of subjects discontinuing from the study was balanced between the treatment arms (14.6% and 12.2% in the QIVc and QIV groups, respectively), as was the proportion of subjects who did not receive the second study vaccine as scheduled (9.7% and 7.7% in the QIVc and QIV groups, respectively). The discontinuations are unlikely to have a major impact on the interpretation of the comparison data.*

6.1.11.5 Exploratory Analyses

The following table displays data from exploratory immunogenicity analyses.

A/H3N2 Immunogenicity Responses Using HAI Assay

Table 26. Immunogenicity Endpoints Using HAI Assay for Cell-Derived Target Virus Strain A/H3N2, Per-Protocol Set

Strain	QIVc N=1089 GMT (95% CI)	QIV N=575 GMT (95% CI)	QIVc N=1092 SCR (95% CI)	QIV N=575 SCR (95% CI)	GMT Ratio (QIV/QIVc)	SCR Difference (QIV%-QIVc%)
A/H3N2 (HAI)	288.1 (261.5, 317.5)	227.6 (201.9, 256.6)	72.3% (69.5, 74.9)	64.5% (60.5, 68.4)	0.8 (0.7, 0.9)	-7.8% (-12.5, -3.1)

Unadjusted GMT values were used for immunogenicity data using MN assay, as the adjusted GMT values could not be estimated for the Asian subpopulation.
Source: Adapted from STN 125408/351, V130_10 Clinical Study Report, Table 14.2.1.1.1 and Table 14.2.2.1.1

Immunogenicity analysis of strain A/H3N2 using HAI assay data for cell-derived target viruses showed non-inferiority of QIVc to QIV with respect to the study success criteria for the primary immunogenicity endpoints.

Reviewer comment: *Despite concerns with the performance of the HAI assay for the H3N2 strain, the GMTs and SCRs appear to be consistent with previous performance of the assay. CBER decided to include the immunogenicity data for strain A/H3N2 using HAI assay data as a footnote in Section 14.4 of the package insert for ease and consistency of interpretation given the medical community's familiarity with the HAI assay as a measure of immunogenicity against influenza. As prespecified, the immunogenicity analyses using MN assay were maintained as the primary immunogenicity endpoint for strain A/H3N2.*

Cell Mediated Immune (CMI) Responses
Eighty subjects between 24 and 47 months of age were enrolled in the CMI population and assessed for CMI response. For CD4+ T-lymphocytes, Staphylococcal enterotoxin B (SEB) antigen stimulation resulted in 1% IL-2, TNF-a, or CD154 positive cells and 0.15% IFN-y or IL-13 positive cells. For CD8+ T-lymphocytes, SEB antigen stimulation resulted in 1% IFN-y or TNF-a positive cells and approximately 0.15% to 0.3% IL-2, IL-13, or CD154 positive cells.

For descriptive bridging purposes, humoral immune responses in the CMI population were assessed and compared to those of the PPS. These analyses showed no notable differences between the groups in responses to A/H1N1 and B/Yamagata. Immune responses to the A/H3N2 strain appeared somewhat higher in the CMI population compared to the PPS. For the B/Victoria strain, immune responses appeared to be lower in the CMI population compared to the PPS.

For descriptive bridging purposes, humoral immune responses in the CMI population were assessed and compared to those of the PPS. These analyses showed no notable differences between the groups in responses to A/H1N1 and B/Yamagata. Immune responses to the A/H3N2 strain appeared somewhat higher in the CMI population compared to the PPS. For the B/Victoria strain, immune responses appeared to be lower in the CMI population compared to the PPS.

Reviewer comment: *The CMI population consists of a small group of subjects (n=58). Although this exploratory analysis was not powered to detect a difference between the CMI and PPS populations, there were no obvious differences between these groups in assessments of humoral immunity that would suggest that the CMI group is substantially different than the PPS for the purpose of immunogenicity comparisons.*

For all endpoints that were evaluated, there were no notable differences between QIVc and QIV for each of the four vaccine strains.

6.1.12 Safety Analyses

6.1.12.1 Methods

Collection of safety data

- Solicited local injection site and systemic adverse reactions were collected using diary cards through Day 7 following vaccination.
    - Solicited (immediate) adverse events were collected for 30 minutes postvaccination.
- All unsolicited adverse events were collected through Day 29 for previously vaccinated subjects, and through Day 57 for subjects not previously vaccinated against influenza.
- SAEs, New Onset Chronic Diseases (NOCDs), AEs leading to withdrawal, and medically attended adverse events were collected through Day 181 for previously vaccinated subjects and through Day 209 for subjects not previously vaccinated.

Safety datasets

- Full Analysis Set (FAS): All subjects randomized and received at least one dose of study vaccination.

- Solicited Safety Set: All subjects in the FAS with any solicited adverse event data.
- Unsolicited Safety Set: All subjects in the FAS with any unsolicited adverse event data.
- Overall Safety Set: All subjects from the Solicited Safety Set and/or the Unsolicited Safety Set. This is the main population for analysis of safety.
    - In the event of vaccination error, subjects were analyzed as "treated" (i.e., the subject was analyzed according to the vaccination they actually received rather than the vaccine to which they were randomized).

6.1.12.2 Overview of Adverse Events

A total of 2414 subjects were enrolled, 2402 of whom were exposed to the study vaccines and included in the Overall Safety Set. The majority of subjects (n=2348; 97.8%) were included in the Solicited Safety Set. No subjects were excluded from the Unsolicited Safety Set.

Solicited Adverse Reactions

The following tables provide solicited adverse reaction data, overall and by selected subgroups.

Reviewer comment: *Subgroup analyses for solicited adverse reactions were conducted for age, sex, race, and history of prior vaccination against influenza. Subgroup analyses emphasized age group as this sBLA will expand approval to the age range of the younger age group (i.e., 6 through 23 months). Subgroup analyses for sex, race, and vaccination history focused on relative incidence of solicited adverse reactions.*

Table 27. Number of Subjects 6 Months Through 47 Months of Age with ≥1 Solicited Adverse Reaction 30 Minutes After Vaccination and/or Day 1 Through Day 7 (Solicited Safety Set)

Solicited Adverse Event	**QIVc** **Any (%) / Grade 3 (%)**	**QIV** **Any (%) / Grade 3 (%)**
Following Any Vaccination Any solicited AE after any vaccination	**N=1564** 997 (63.7)	**N=784** 517 (65.9)
30 Minutes After Any Vaccination Any Local Systemic Analgesic/Antipyretic Use	-- 192 (12.3%) 171 (10.9%) 30 (1.9%) 8 (0.5%)	-- 104 (13.3%) 95 (12.1%) 18 (2.3%) 2 (0.3%)
Day 1 Through Day 7 After Any Vaccination Any Local Systemic Analgesic/Antipyretic Use	-- 940 (60.1%) 656 (41.9%) 681 (43.5%) 240 (15.3%)	-- 491 (62.6%) 350 (44.6%) 358 (45.7%) 136 (17.3%)
After Vaccination 1 Any solicited AE after Vaccination 1	**N=1564** 934 (59.7)	**N=784** 490 (62.5)

Solicited Adverse Event	QIVc Any (%) / Grade 3 (%)	QIV Any (%) / Grade 3 (%)
30 Minutes After Vaccination 1	--	--
Any	163 (10.4)	90 (11.5)
Local	146 (9.3)	81 (10.3)
Systemic	25 (1.6)	15 (1.9)
Analgesic/Antipyretic Use	5 (0.3)	1 (0.1)
Day 1 Through Day 7 After Vaccination 1	--	--
Any	882 (56.4)	465 (59.3)
Local	619 (39.6)	325 (41.5)
Systemic	625 (40.0)	328 (41.8)
Analgesic/Antipyretic Use	197 (12.6)	117 (14.9)
After Vaccination 2	**N=698**	**N=340**
Any solicited AE after Vaccination 2	328 (47.0)	159 (46.8)
30 Minutes After Vaccination 2	--	--
Any	56 (8.0)	27 (7.9)
Local	48 (6.9)	26 (7.6)
Systemic	7 (1.0)	4 (1.2)
Analgesic/Antipyretic Use	4 (0.6)	1 (0.3)
Day 1 Through Day 7 After Vaccination	--	--
Any	307 (44.0)	148 (43.5)
Local	173 (24.8)	89 (26.2)
Systemic	235 (33.7)	110 (32.4)
Analgesic/Antipyretic Use	70 (10.0)	38 (11.2)

Source: Adapted from STN 125408/351, Study V130_10 CSR, Table 12-2, p. 133-134

Table 28. Incidence of Solicited Local and Systemic Adverse Reactions and Proportion of Grade 3 Severity After Dose 1, Dose 2, and Any Vaccination in Subjects 6 Months Through 47 Months of Age in the Solicited Safety Set

	QIVc (N=1564) Any (%) / Grade 3 (%)	QIVc (N=1564) Any (%) / Grade 3 (%)	QIVc (N=1564) Any (%) / Grade 3 (%)	QIV (N=784) Any (%) / Grade 3 (%)	QIV (N=784) Any (%) / Grade 3 (%)	QIV (N=784) Any (%) / Grade 3 (%)
	After Dose 1 (N=1564)	**After Dose 2 (N=698)**	**After Any Dose (N=1564)**	**After Dose 1 (N=784)**	**After Dose 2 (N=340)**	**After Any Dose (N=784)**
Local Adverse Reactions						
Tenderness	25.4 / 1.9	15.5 / 1.1	27.9 / 2.2	27.6 / 1.3	16.5 / 0	18.3 / 1.4
Erythema	23.9 / 0.4	14.2 / 0	25.8 / 0.4	22.6 / 0	13.5 / 0	24.6 / 0
Induration	15.1 / 0.4	9.2 / 0	17.3 / 0.4	13.9 / 0	10.6 / 0	15.9 / 0
Ecchymosis	9.6 / 0.1	5.2 / 0.1	10.7 / 0.1	9.4 / 0	5.3 / 0	10.8 / 0
Systemic Adverse Reactions						
Irritability	24.6 / 2.2	22.2 / 2.6	27.9 / 3.1	26.0 / 2.0	20.6 / 2.1	29.6 / 2.7
Sleepiness	23.3 / 1.5	20.9 / 1.6	26.9 / 2.1	22.3 / 1.0	16.8 / 0.9	25.5 / 1.4
Diarrhea	14.4 / 1.0	14.2 / 1.4	17.9 / 1.6	13.9 / 0.6	12.1 / 0.9	16.3 / 1.0
Change of Eating Habits	14.1 / 1.1	12.3 / 1.1	17.4 / 1.5	14.8 / 1.0	11.8 / 1.5	17.6 / 1.7
Fever	5.2 / 0.4	4.7 / 0.6	6.8 / 0.6	5.0 / 0.1	5.6 / 0	6.9 / 0.1
Vomiting	5.3 / 0.4	4.6 / 0.4	6.8 / 0.6	5.0 / 0.5	3.5 / 0	6.3 / 0.5
Shivering	2.6 / 0.2	1.4 / 0	3 / 0.2	2.9 / 0	2.1 / 0	3.4 / 0

Grade 3 local adverse reactions: Tenderness: "cried when limb was moved/spontaneously painful" in subjects 6 through 23 months and "prevents daily activity" in subjects 24 through 47 months, Erythema, Induration, or Ecchymosis: ≥50 mm diameter.
Grade 3 systemic adverse reactions: Fever: ≥102.2ºF, Change of eating habits: missed more than two feeds/meals, Sleepiness: sleeps most of the time and is hard to arouse, Vomiting: six or more times in 24 hours or requires IV hydration, Diarrhea: six or more stools in 24 hours or requires IV hydration, Irritability: unable to console. Grade 3 for all other adverse reactions is that which prevents daily activity.
Source: Adapted from STN 125408/351, Study V130_10 CSR, Table 14.3.3 and Table 12-4 and 12-5, p. 138-139 and p. 146-149

The mean time of onset of induration, erythema, ecchymosis, and tenderness after any vaccination ranged from 1.1 to 1.4 days in the QIVc group and from 1.1 to 1.4 days in the QIV group. The mean time of onset of each solicited systemic adverse event after any vaccination ranged from 1.6 to 3.1 days in the QIVc group and from 1.5 to 3.1 days in the QIV group.

The most frequent local solicited adverse reactions during this study were tenderness and erythema of the injection site, and the most frequent systemic solicited adverse reactions were irritability and sleepiness (Table 28, above). The incidence of fever was balanced between QIVc recipients and QIV recipients with 6.8% and 6.9%, respectively, after any vaccination. Subjects who received QIVc had a slightly higher rates of adverse reactions that were Grade 3 or higher compared to subjects who received QIV. The rate of solicited adverse reactions was generally lower following the second dose of QIVc or QIV compared to the first dose.

Injection site tenderness occurred more commonly among QIVc recipients compared to QIV recipients. Other than injection site tenderness, the proportion of subjects with local and systemic adverse reactions was comparable between treatment groups.

The mean time to onset of solicited local and systemic adverse reactions was comparable between QIVc and QIV recipients. The proportion of subjects that continued to report local or systemic solicited adverse reactions decreased in each group; however, a higher proportion of QIVc recipients continued to experience solicited adverse reactions beyond Day 7 as described below.

Solicited Adverse Reactions Persisting Beyond Day 7 After Vaccination

The proportions of subjects with local adverse reactions persisting beyond 7 days after vaccination ranged from 0.3% to 1.0% in the QIVc group and between 0.1% to 1.1% in the QIV group. The proportions of subjects with systemic adverse reactions persisting beyond 7 days after vaccination ranged from 0.3% to 2.3% in the QIVc group and between 0.1% to 1.5% in the QIV group.

Table 29. Number of Subjects 6 Months Through 47 Months of Age with ≥1 Solicited Adverse Reaction Persisting Beyond 7 Days After Vaccination in the Solicited Safety Set

	QIVc (N=1564) n (%)	QIV (N=784) n (%)
Local Adverse Reactions		
Ecchymosis	15 (1%)	9 (1.1%)
Erythema	10 (0.8%)	2 (0.3%)
Induration	12 (0.5%)	5 (0.6%)
Tenderness	5 (0.3%)	1 (0.1%)
Systemic Adverse Reactions		
Diarrhea	36 (2.3%)	12 (1.3%)
Irritability	27 (1.7%)	11 (1.4%)
Fever	23 (1.5%)	8 (1%)
Change of Eating Habits	21 (1.3%)	11 (1.4%)
Sleepiness	19 (1.2%)	5 (0.6%)
Vomiting	10 (0.6%)	3 (0.4%)
Shivering	4 (0.3%)	1 (0.1%)

Source: Adapted from STN 125408/351, Study V130_10 CSR, Table 14.3.7.

Reviewer comment: *QIVc recipients appeared to have slightly higher rates of reactogenicity persisting beyond 7 days after vaccination relative to QIV recipients. The greater number of solicited adverse events that persisted beyond Day 7 in the QIVc group may be attributed to the higher antigen dose in QIVc for children <3 years of age.*

Solicited Adverse Reactions by Age

Table 30. Percentage of Subjects with ≥1 Solicited Adverse Reaction and Percentage of Adverse Reactions That Are Grade 3 or Higher by Age from Day 1 Through Day 7 After Any Vaccination in the Solicited Safety Set

	6 Months Through 23 Months	6 Months Through 23 Months	24 Months Through 47 Months	24 Months Through 47 Months
	QIVc, N=581 Any (%) / Grade 3 (%)	QIV, N=292 Any (%) / Grade 3 (%)	QIVc, N=93 Any (%) / Grade 3 (%)	QIV, N=492 Any (%) / Grade 3 (%)
Local Adverse Reactions				
Tenderness	25.5 / 2.1	23.3 / 1.4	29.3 / 2.2	33.9 / 1.4
Erythema	25.3 / 0	18.2 / 0	26.0 / 0.7	28.5 / 0
Induration	16.5 / 0.5	12.0 / 0	17.7 / 0.3	18.3 / 0
Ecchymosis	11.2 / 0.2	7.5 / 0	10.5 / 0.1	12.8 / 0
Systemic Adverse Reactions				
Sleepiness	35.5 / 2.4	30.5 / 1.7	21.8 / 1.9	22.6 / 1.2
Irritability	35.1 / 5.2	35.6 / 2.1	23.6 / 1.8	26.0 / 3.0
Diarrhea	23.2 / 2.4	20.2 / 0.7	14.8 / 1.1	14.0 / 1.2
Change of eating habits	21.0 / 1.7	21.9 / 2.4	15.3 / 1.4	15.0 / 1.2
Fever	9.3 / 0.7	10.3 / 0	5.4 / 0.6	4.8 / 0.2
Vomiting	10.5 / 0.7	6.8 / 0.7	4.6 / 0.5	5.9 / 0.4
Shivering	3.1 / 0.2	3.1 / 0	3.3 / 0.2	3.7 / 0

Grade 3 local adverse reactions: Tenderness: "cried when limb was moved/spontaneously painful" in subjects 6 through 23 months and "prevents daily activity" in subjects 24 through 47 months, Erythema, Induration, or Ecchymosis: ≥50 mm diameter.
Grade 3 systemic adverse reactions: Fever: ≥102.2ºF, Change of eating habits: missed more than two feeds/meals, Sleepiness: sleeps most of the time and is hard to arouse, Vomiting: six or more times in 24 hours or requires IV hydration, Diarrhea: six or more stools in 24 hours or requires IV hydration, Irritability: unable to console. Grade 3 for all other adverse reactions is that which prevents daily activity.
Source: Adapted from STN 125408/351, Study V130_10 CSR, Table 14.3.3.3

Reviewer comment: *Consistent with reactogenicity patterns observed in other vaccine trials, there was a higher rate of solicited systemic adverse reactions among the younger age group of subjects that received QIVc or QIV (52.5% vs 38.3% and 53.4% vs 41.1%, respectively). The rates of systemic adverse reactions are generally balanced between subjects who received QIVc vs the comparator vaccine. In the younger age group, QIVc recipients had a higher rate of Grade 3 systemic adverse reactions than QIV recipients (i.e., irritability 5.2% vs 2.1%, sleepiness 2.4% vs 1.7%, diarrhea 2.4% vs 0.7%).*

There were no notable differences in the rates of solicited local adverse reactions among subjects 6 months through 23 months of age who received QIVc vs QIV, with a rate of reported local adverse reactions of 41.3% vs 36%, respectively. QIVc recipients had a higher rate of Grade 3 injection site tenderness compared to QIV recipients in both age groups (2.1 - 2.2% vs 1.4%)

Solicited Adverse Reactions by Influenza Vaccination History

Table 31. Subjects with ≥1 Solicited Adverse Reaction By Influenza Vaccination History From Day 1 Through Day 7 After Vaccination in the Solicited Safety Set

	QIVc n/N (%)	QIV n/N (%)	Overall
Previously Vaccinated	480/794 (60.5%)	270/419 (64.4%)	750/1213 (61.8%)
Vaccine naïve	46/770 (59.7%)	221/365 (60.5%)	681/1135 (60%)

n = Number of subjects who experienced a solicited adverse reaction within a given subset
N = Total number of subjects in a subset by treatment arm and vaccination status
Source: Adapted from STN 125408/351, Study V130_10 CSR, Table 14.3.3.2

Subjects previously vaccinated against influenza who received QIVc had comparable rates of solicited adverse reactions to previously vaccinated subjects who received QIVc. Similarly, influenza vaccine-naïve subjects who received QIVc had comparable rates of solicited adverse reactions to influenza vaccine-naïve subjects who received QIV. The overall rate of solicited adverse reactions was comparable between subjects previously vaccinated against influenza and influenza vaccine-naïve subjects.

Solicited Adverse Reactions by Sex

Table 32. Subjects with ≥1 Solicited Local and/or Systemic Adverse Reaction By Sex From Day 1 Through Day 7 After Vaccination (Solicited Safety Set)

	QIVc n/N (%)	QIV n/N (%)	Overall
Male	485/787 (61.6%)	254/397 (64%)	739/1184 (62.4%)
Female	455/777 (58.6%)	237/387 (61.2%)	692/1164 (59.5%)

n = Number of subjects who experienced a solicited adverse reaction within a given subset
N = Total number of subjects in a subset by treatment arm and sex
Source: Adapted from STN 125408/351, Study V130_10 CSR, Table 14.3.3.4

The proportion of subjects with at least one solicited adverse reaction was comparable between male and female subjects.

Solicited Adverse Reactions by Race

Table 33. Subjects with ≥1 Solicited Adverse Reaction By Race From Day 1 Through Day 7 After Vaccination in the Solicited Safety Set

	QIVc n/N (%)	QIV n/N (%)	Overall
White	687/1027 (66.9%)	364/531 (68.5%)	1051/1558 (67.5%)
Black or African American	185/439 (42.1%)	88/196 (44.9%)	273/635 (43%)
Asian	9/13 (69.2%)	4/8 (50%)	13/21 (61.9%)
Native Hawaiian or Pacific Islander	6/8 (75%)	4/6 (66.7%)	10/14 (71.4%)
American Indian or Alaska Native	9/11 (81.8%)	7/11 (63.6%)	16/22 (72.7%)

	QIVc n/N (%)	QIV n/N (%)	Overall
Other	44/66 (66.7%)	24/32 (75%)	68/98 (69.4%)

n = Number of subjects who experienced a solicited adverse reaction within a given subset
N = Total number of subjects in a subset by treatment arm and race
Source: Adapted from STN 125408/351, Study V130_10 CSR, Table 14.3.3.5

Reviewer comment: *The rate of vaccine reactogenicity is higher in subjects who are Asian, Native Hawaiian or Pacific Islander and American Indian or Alaska Native. However, interpretation of these differences is confounded by the small number of subjects in some of the Race subgroups.*

Unsolicited Adverse Events
Overall, any unsolicited AE after any vaccination through Day 29/57 was reported by 26.2% of subjects after QIVc and 25.7% of subjects after QIV.

Table 34. Number and Proportion of Subjects with Any or at Least Possibly Related Unsolicited Adverse Events with Onset from Day 1 Through Day 29/57 by Preferred Term, Occurring with ≥1% Frequency in Any Group

	All Causality AEs	All Causality AEs	AEs at Least Possibly Related	AEs at Least Possibly Related
	QIVc, n (%) (N=1597)	QIV, n (%) (N=805)	QIVc, n (%) (N=1597)	QIV, n (%) (N=805)
Any	418 (26.2)	207 (25.7)	70 (4.4)	36 (4.5)
Gastrointestinal Disorders				
Diarrhoea	43 (2.7)	18 (2.2)	11 (0.7)	3 (0.4)
Vomiting	22 (1.4)	8 (1.0)	2 (0.1)	0
General Disorders and Administration Site Conditions				
Pyrexia	46 (2.9)	25 (3.1)	5 (0.3)	3 (0.4)
Injection site bruising	15 (0.9)	9 (1.1)	13 (0.8)	8 (1.0)
Infections and Infestations				
Upper respiratory tract infection	59 (3.7)	44 (5.5)	2 (0.1)	0
Otitis media	28 (1.8)	13 (1.6)	0	0
Ear infection	15 (0.9)	10 (1.2)	1 (0.1)	0
Nervous System Disorders				
Somnolence	19 (1.2)	6 (0.7)	7 (0.4)	2 (0.2)
Psychiatric Disorders				
Irritability	24 (1.5)	14 (1.7)	12 (0.8)	6 (0.7)

	All Causality AEs	All Causality AEs	AEs at Least Possibly Related	AEs at Least Possibly Related
	QIVc, n (%) (N=1597)	QIV, n (%) (N=805)	QIVc, n (%) (N=1597)	QIV, n (%) (N=805)
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	43 (2.7)	23 (2.9)	2 (0.1)	2 (0.2)
Rhinorrhoea	36 (2.3)	17 (2.1)	11 (0.4)	3 (0.4)
Nasopharyngitis	19 (1.2)	14 (1.7)	0	0

Source: Adapted from STN 125408/351, Study V130_10 CSR, Table 14.3.8.3.2

Reviewer comment: *The majority of AEs considered at least possibly related to QIVc were reactogenicity events that are consistent with the known safety profile of influenza vaccines. The remaining AEs considered at least possibly related to QIVc consist of a small number of conditions that are common in this age group (e.g., rhinorrhea, cough) and do not represent a safety concern related to QIVc.*

Between Day 1 and Day 29/57, 14 subjects experienced a total of 16 unsolicited AEs that were Grade 3 or higher. Twelve (0.8%) of these subjects were QIVc recipients and 2 (0.2%) were QIV recipients.

Grade 3 events included: irritability, seizure, asthma, pneumonia, hand-foot-and-mouth disease, ligamentitis, road traffic accident, adenoviral encephalitis, nasopharyngitis, dehydration, volvulus, bronchiolitis, tibia fracture, acute respiratory failure, respiratory syncytial virus infection, and oral herpes. Of these Grade 3 events, six were non-serious, including irritability, hand-foot-and-mouth disease, nasopharyngitis, dehydration, tibia fracture, and oral herpes. Only the event of dehydration was considered possibly related. The SAEs are further discussed in Sections 6.1.12.3 (Deaths) and 6.1.12.5 (Nonfatal Serious Adverse Events).

Reviewer comment: *The incidences of unsolicited AEs between Day 1 and Day 29/57 were similar between subjects who received QIVc and QIV. The pattern of reported events was consistent with medical conditions typically experienced by this pediatric population. Vaccine-naïve subjects had slightly higher rates of mild respiratory, thoracic, and mediastinal disorders as well as mild infections and infestations; however, these differences were balanced between study arms. There were no notable differences in the severity of unsolicited adverse events between previously vaccinated subjects and vaccine-naïve subjects.*

Subjects in the younger age group (6 through 23 months) had a higher incidence of infections and infestations compared to subjects in the older age group, though these differences were balanced between subjects who received QIVc and subjects who received QIV. The increased frequency of infections and infestations was primarily driven by upper respiratory tract infections and otitis media, which are common in the general pediatric population.

Medically Attended Adverse Events
Overall, MAAEs were reported by 13.9% of subjects in the QIVc group and 12.0% of subjects in the QIV group.

Table 35. Medically Attended Adverse Events (MAAEs) Through Study Completion by System Organ Class and Preferred Term, Occurring with ≥1% Frequency in Any Group

System Organ Class - Preferred Term	QIVc (n=1597) n (%)	QIV (n=805) n (%)
Gastrointestinal disorders	**23 (1.4)**	**6 (0.7)**
General disorders and administration site conditions	**15 (0.9)**	**10 (1.2)**
Pyrexia	15 (0.9)	10 (1.2)
Infections and infestations	**175 (11.0)**	**72 (8.9)**
Influenza	18 (1.1)	4 (0.5)
Otitis media	35 (2.2)	17 (2.1)
Pharyngitis streptococcal	13 (0.8)	9 (1.1)
Upper respiratory tract infection	36 (2.3)	22 (2.7)
Respiratory, thoracic and mediastinal disorders	**29 (1.8)**	**13 (1.6)**
Skin and subcutaneous tissue disorders	**23 (1.4)**	**8 (1.0)**

Source: (b) (4)
Filters: TRT01A = "Seqirus QIVc" and SAFFL = "Y" (QIVc); TRT01A = "Comparator QIV" and SAFFL = "Y" (QIV); TRTEMFL = "Y" and MAAE = "Y" (Adverse Events).
Percent Threshold: Any Column ≥1%.

Reviewer comment: *There is a slightly increased rate of medically attended infections and infestations among subjects who received QIVc compared to subjects who received QIV; however, this is based on a small number of cases that were temporally remote from administration of the study vaccine. It is unlikely that this imbalance of infections and infestations is related to the study vaccine.*

New Occurrence of Chronic Diseases
Overall, AEs leading to NOCDs were reported by 1.4% of subjects in the QIVc group and 1.6% of subjects in the QIV group.

Table 36. New Occurrence of Chronic Diseases Through Study Completion by System Organ Class and Preferred Term

System Organ Class - Preferred Term	QIVc (N=1597) n (%)	QIV (N=805) n (%)
Blood and lymphatic system disorders	**1 (0.1)**	**0 (0.0)**
Iron deficiency anaemia	1 (0.1)	0 (0.0)
Eye disorders	**1 (0.1)**	**0 (0.0)**
Conjunctivitis allergic	1 (0.1)	0 (0.0)
Gastrointestinal disorders	**2 (0.1)**	**2 (0.2)**
Constipation	1 (0.1)	1 (0.1)
Diarrhoea	1 (0.1)	0 (0.0)
Teething	0 (0.0)	1 (0.1)

System Organ Class - Preferred Term	QIVc (N=1597) n (%)	QIV (N=805) n (%)
Immune system disorders	**3 (0.2)**	**1 (0.1)**
Food allergy	1 (0.1)	0 (0.0)
Seasonal allergy	2 (0.1)	1 (0.1)
Infections and infestations	**4 (0.3)**	**2 (0.2)**
Ear infection	2 (0.1)	1 (0.1)
Otitis media chronic	1 (0.1)	0 (0.0)
Tonsillitis streptococcal	1 (0.1)	0 (0.0)
Upper respiratory tract infection	0 (0.0)	1 (0.1)
Investigations	**1 (0.1)**	**2 (0.2)**
Cardiac murmur	0 (0.0)	2 (0.2)
Cardiac murmur functional	1 (0.1)	0 (0.0)
Nervous system disorders	**1 (0.1)**	**0 (0.0)**
Seizure like phenomena	1 (0.1)	0 (0.0)
Psychiatric disorders	**0 (0.0)**	**2 (0.2)**
Attention deficit hyperactivity disorder	0 (0.0)	1 (0.1)
Insomnia	0 (0.0)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	**6 (0.4)**	**3 (0.4)**
Asthma	3 (0.2)	1 (0.1)
Cough	1 (0.1)	0 (0.0)
Cough variant asthma	1 (0.1)	0 (0.0)
Rhinitis allergic	0 (0.0)	1 (0.1)
Rhinorrhoea	1 (0.1)	0 (0.0)
Sleep apnoea syndrome	0 (0.0)	1 (0.1)
Tonsillar hypertrophy	1 (0.1)	0 (0.0)
Skin and subcutaneous tissue disorders	**5 (0.3)**	**2 (0.2)**
Alopecia	1 (0.1)	0 (0.0)
Dermatitis atopic	2 (0.1)	0 (0.0)
Eczema	1 (0.1)	1 (0.1)
Eczema nummular	0 (0.0)	1 (0.1)
Urticaria	1 (0.1)	0 (0.0)

Source: (b) (4) .
Filters: TRT01A = "Seqirus QIVc" and SAFFL = "Y" (QIVc); TRT01A = "Comparator QIV" and SAFFL = "Y" (QIV); TRTEMFL = "Y" and NOCD = "Y" (Adverse Events).

There was an overall low incidence of new onset chronic diseases, and the frequency of new onset chronic diseases was balanced between arms. There were no notable differences between subjects who received QIVc compared to those who received QIV.

6.1.12.3 Deaths

There were two reported deaths during the study in the QIVc group. One death occurred in a 22-month-old female at the time of enrollment who was involved in a fatal traffic accident on Day (b) (6) days after administration of the second study vaccine.

Reviewer comment*: This fatal event had a clear alternative etiology that was unrelated to vaccination. The Applicant and the investigator assessed this event as not related to the study vaccine. This reviewer agrees that this event was unrelated to vaccination.*

The second death occurred in a previously healthy 7-month-old male at the time of enrollment who developed status epilepticus secondary to presumed adenovirus-related encephalopathy. The subject became febrile without other associated symptoms on Day

56 (b) (6) days after the second study vaccination). On Day 57, the subject was brought to the emergency department because of status epilepticus which lasted approximately 45 minutes. He was febrile to 39.9 ºC and hypoxic upon arrival to the emergency department. He was intubated but developed bradycardic respiratory arrest immediately following intubation, requiring eleven minutes of cardiopulmonary resuscitation. An intranasal swab was sent for multiplex polymerase chain reaction (PCR) assay of respiratory viruses and returned positive for adenovirus. A lumbar puncture was performed and showed no cerebrospinal fluid (CSF) pleiocytosis or hypoglycorrhachia. His CSF culture was negative, as were PCR assays for enterovirus, HSV-1, and HSV-2 from the CSF. An adenovirus PCR assay of the CSF was not performed. The subject's hospital course was complicated by cerebral edema secondary to hypoxic ischemic encephalopathy. Magnetic resonance imaging of the brain demonstrated evidence of increased intracranial pressure with mild cerebellar tonsillar herniation; however, there were no inflammatory changes of the brain parenchyma or the meninges. His neurological status failed to improve and brain death was declared on Day (b) (6)

Reviewer comment: *This subject developed a clinical syndrome consisting of fever, prolonged seizure, and neurological sequelae (b) (6) days after receipt of the second dose of QIVc. The acute onset of fever preceding the development of status epilepticus may suggest an infectious etiology such as viral encephalitis; however, a definitive pathogenic organism (i.e., an infectious organism isolated from the CSF) was not identified during this subject's diagnostic evaluation. Given the prodrome of fever before the onset of status epilepticus, it is also plausible that this subject had an undiagnosed comorbidity (e.g., genetic epilepsy syndrome, inborn error of metabolism) that was precipitated by the inflammatory insult of an adenovirus respiratory infection. The Applicant and investigator assessed this event as not related to the study vaccine. An independent data monitoring committee (convened for another pediatric influenza vaccine study) reviewed this case and assessed this event as not related to the study vaccine.*

While no definitive alternative diagnosis was established for this subject and a causal relationship to QIVc cannot be excluded, this reviewer agrees that it is unlikely that this event was related to administration of QIVc. The (b) (6) -day latency period is longer than the duration expected based on existing data of vaccine-associated seizures, and clinical syndromes of this character and severity have not been associated with the licensed seasonal influenza vaccines to date. The absence of inflammatory changes of the brain parenchyma and meninges also make vaccine-associated seizures less likely in this scenario. Please see Section 6.1.12.4 Nonfatal Serious Adverse Events for further assessment of seizures that occurred during this study.

6.1.12.4 Nonfatal Serious Adverse Events

There were 19 SAEs among 15 (0.9%) QIVc recipients and 7 SAEs among 7 (0.9%) comparator vaccine recipients. SAEs were most frequently reported in the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class of Infections and infestations, with 10 (0.6%) SAEs reported among QIVc recipients and 3 (0.4%) SAEs reported among comparator vaccine recipients. The most common SAEs included pneumonia, bronchiolitis, and other respiratory viral infections. None of the SAEs were considered related to the study vaccine by the investigator.

Table 37. Serious Adverse Events by System Organ Class and Preferred Term (Unsolicited Safety Set)

System Organ Class - Preferred Term	QIVc (N=1597) n (%)	QIV (N=805) n (%)
Gastrointestinal disorders	**1 (0.1)**	**1 (0.1)**
Constipation	0 (0.0)	1 (0.1)
Volvulus	1 (0.1)	0 (0.0)
Infections and infestations	**10 (0.6)**	**3 (0.4)**
Abscess of eyelid	1 (0.1)	0 (0.0)
Adenoviral encephalitis	1 (0.1)	0 (0.0)
Bronchiolitis	1 (0.1)	3 (0.4)
Enterovirus infection	1 (0.1)	0 (0.0)
Metapneumovirus infection	0 (0.0)	1 (0.1)
Pneumonia	3 (0.2)	0 (0.0)
Pneumonia bacterial	1 (0.1)	0 (0.0)
Respiratory syncytial virus bronchiolitis	1 (0.1)	0 (0.0)
Respiratory syncytial virus infection	1 (0.1)	0 (0.0)
Rhinovirus infection	1 (0.1)	1 (0.1)
Injury, poisoning and procedural complications	**1 (0.1)**	**0 (0.0)**
Road traffic accident	1 (0.1)	0 (0.0)
Metabolism and nutrition disorders	**1 (0.1)**	**1 (0.1)**
Dehydration	1 (0.1)	1 (0.1)
Musculoskeletal and connective tissue disorders	**1 (0.1)**	**0 (0.0)**
Ligamentitis	1 (0.1)	0 (0.0)
Nervous system disorders	**2 (0.1)**	**1 (0.1)**
Seizure	2 (0.1)	0 (0.0)
Unresponsive to stimuli	0 (0.0)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	**3 (0.2)**	**1 (0.1)**
Acute respiratory failure	1 (0.1)	0 (0.0)
Asthma	2 (0.1)	1 (0.1)

Source: (b) (4)
Filters: TRT01A = "Seqirus QIVc" and SAFFL = "Y" (QIVc); TRT01A = "Comparator QIV" and SAFFL = "Y" (Comparator QIV); TRTEMFL = "Y" and AESER = "Y" (Adverse Events).
Source: STN 125408/351, V130_10 Clinical Study Report, Table 14.3.8.4.1

Reviewer comment: *There is an apparent imbalance between instances of pneumonia between QIVc recipients (four cases) and comparator recipients (zero cases).*

Details of these SAEs are included in the table below:

Table 38. Serious Events of Pneumonia Among Subjects Randomized to QIVc

Unique Subject ID	Subject Age	Time from last Vaccination (Dose Number)	Subject Risk Factors	Month of Diagnosis
(b) (6)	42 months	22 days (Dose 1)	Asthma (new diagnosis)	October
	43 months	69 days (Dose 1)	Asthma	December
	9 months	63 days (Dose 2)	None	December
	21 months	37 days (Dose 2)	Atopy, sinusitis	November

Source: Adapted from STN 125408.351, Study V130_10 SAE Narratives

Reviewer comment: *Although there was a disproportionate number of subjects with serious events of pneumonia in the QIVc group, there is no strong or consistent temporal relationship to relate these events to administration of the study vaccine. Three of the four (75%) subjects had underlying comorbidities (i.e., asthma or other atopy) which could potentially predispose these subjects to invasive respiratory infections.[11] These SAEs occurred between October and December, which are months associated with higher incidence of invasive infectious respiratory diseases such as bacterial pneumonia in children. This reviewer agrees that these events of bacterial pneumonia are not related to the study vaccine.*

Three serious events of seizure occurred among subjects randomized to QIVc, including the subject with a fatal event of adenoviral encephalitis discussed in Section 6.1.12.3. Details of each event are listed below:

Table 39. Serious Events of Seizure Among Subjects Randomized to QIVc

Unique Subject ID	Subject Age	Time from Vaccination (Dose Number)	Details of the Event
(b) (6)	22 months	17 days (Dose 1)	Subject was well until new onset abnormal focal movements of the right upper extremity with secondary generalization lasting several minutes. Seizure resolved spontaneously but a second seizure lasting six minutes occurred following arrival to the emergency department, requiring intravenous lorazepam. There was no fever or other preceding symptoms. The subject withdrew from the study approximately one month later. The investigator and Applicant assessed this event as unrelated to the study vaccine.
	7 months	(b) (6) days (Dose 2)	Previously healthy 7-month-old subject who developed fever and subsequently went into status epilepticus the following day. The subject developed hypoxic ischemic encephalopathy with cerebral edema as a consequence of his illness, with a fatal outcome. Please see Section 6.1.12.3 for details of this fatal event.
	40 months	168 days (Dose 1)	Subject had history of periventricular hemorrhage and spastic hemiplegic cerebral palsy. Subject hit his head at the playground without loss of consciousness. The subject was taken to the hospital by ambulance and during transit was noted to be seizing which stopped after 10 minutes following administration of midazolam. He developed post-ictal somnolence but was appropriately responsive following this event. He was discharged from the emergency department with outpatient neurology follow-up. The investigator and the Applicant assessed this event as unrelated to the study vaccine.

Reviewer comment: *While a definitive alternative etiology was not established for Subject* (b) (6) *, this reviewer agrees that the latency period of 17 days without other symptoms in the interim makes it unlikely that this subject's seizures were related to QIVc. Vaccine-associated seizures typically have a shorter latency period between vaccination and the onset of seizures. In addition, children with epilepsy in this age group are known to develop first-time seizure activity without a clearly identified etiology. While a causal relationship between vaccination and the onset of seizures cannot be excluded, this reviewer agrees with the Applicant's assessment that this subject's seizures were unlikely to be related to QIVc.*

Subject (b) (6) *seizure event had a distant temporal relationship to vaccination. The combination of this subject's history of periventricular hemorrhage, spastic hemiplegic cerebral palsy, and antecedent head trauma are likely to have contributed to the onset of seizure. This reviewer agrees that this subject's seizure was related to QIVc.*

Subject (b) (6) *was a 15-month-old female who was diagnosed with seizure like phenomena on Day 181, 152 days after the second dose of QIVc. The event was considered non-serious and moderate in severity. The Applicant and the investigator assessed this event as not related to the study vaccination. This reviewer agrees that this event is unlikely to be related given the prolonged latency period between this event and the time of vaccination.*

An information request was submitted to the Applicant on September 3, 2021 requesting that further safety review of seizure events after vaccination be performed, including searches of the clinical development and postmarketing safety databases for events of seizures/convulsions.

The Applicant performed a narrow Standardized MedDRA Query for "generalized convulsive seizures following immunization." Individual Case Safety Reports (ICSRs) were stratified by age, with the youngest age cohort including children 6 months to 9 years of age. Six ICSRs were identified: two occurred during V130_10 and four were reported spontaneously. The two ICSRs from Study V130_10 were for subjects (b) (6) *, and these events are described above. The spontaneously reported ICSRs included a 4-year-old female with autism spectrum disorder who developed three febrile seizures one day after receipt of QIVc, Proquad, and Kinrix. Two ICSRs included a 7-year-old female and a 7-year-old male each with current diagnoses of epilepsy who had a seizure 4 days after vaccination and on the day of vaccination, respectively. The final ICSR in this age group was a 6-year-old female who fell to the floor within one minute of receipt of QIVc. She reportedly had seizure activity lasting one minute; however, she had complete recovery to her baseline following this event. The Applicant assessed this event as an anxiety reaction to vaccination. This reviewer agrees that this event is likely psychosomatic in nature or represents postvaccination vasovagal syncope.*

While there was a larger number of SAEs involving seizures among the QIVc recipients, each individual event was unlikely to be related to receipt of QIVc. Therefore, the SAEs described above do not represent a concerning safety signal related to QIVc.

The narratives for all of the remaining SAEs were reviewed, and none were considered related to the study vaccine by the Applicant. This reviewer agrees with the Applicant's final diagnosis and assessment of vaccine relatedness for each event.

6.1.12.5 Adverse Events of Special Interest (AESI)

Adverse Events of Special Interest were not defined for this study.

6.1.12.6 Clinical Test Results

No routine safety laboratory assessments were performed as part of this study.

6.1.12.7 Dropouts and/or Discontinuations

Table 40. Subject Disposition

	QIVc (n=1605)	**QIV (n=809)**
Number Enrolled	1605 (100%)	809 (100%)
Number Vaccinated	1597 (99.5%)	805 (99.5%)
Completed Protocol	1370 (85.4%)	710 (87.8%)
Discontinuation due to:		
Adverse Event	1 (0.1%)	0
Death	2 (0.1%)	0
Withdrawal of Consent	36 (2.2%)	16 (2%)
Protocol deviation	0	0
Other	5 (0.3%)	7 (0.9%)

Source: Adapted from STN 125408/351, V130_10 Clinical Study Report, Table 10-1, p. *81*

There were two non-serious AEs which resulted in vaccine discontinuation. One subject was a 40-month-old, influenza vaccine-naïve male who developed Grade 2 loss of appetite 2 days after administration of QIVc. This subject was withdrawn from the second dose of QIVc; however, he remained enrolled for safety follow-up. His change of appetite resolved within 7 days. The investigator assessed this event as possibly related to QIVc. The other subject was an 11-month-old male who developed a diffuse rash 27 days after receipt of QIV. The subject was diagnosed with a viral exanthem. This AE resulted in withdrawal of the second dose of QIV. The Applicant and investigator assessed this event as not related to the comparator vaccine.

One SAE resulted in study discontinuation. Subject V130-10-(b) (6), a 22-month-old male subject, developed seizure activity 17 days after the first dose of the study vaccine. Please see Section 6.1.12.4 Other Serious Non-Fatal Adverse Events for further discussion of this case.

Reviewer comment: *These subject discontinuations did not significantly impact the interpretation of the safety or immunogenicity data for V130_10. Please see Section 6.1.10.1.3 Subject Disposition for further discussion of subject discontinuations.*

6.1.13 Study Summary and Conclusions

Immune responses elicited by QIVc were measured using GMTs and SCRs at Day 29 for previously vaccinated subjects and Day 57 for vaccine-naïve subjects, using HAI assay for strains A/H1N1, B/Yamagata, and B/Victoria and MN assay for strain A/H3N2. Cell-derived target viruses were used for analyses of primary immunogenicity endpoints. Postvaccination GMT ratios with 95% confidence intervals for A/H1N1, A/H3N2,

B/Yamagata, and B/Victoria were 0.73 (0.65, 0.84), 1.04 (0.93, 1.16), 0.73 (0.66, 0.81), and 0.88 (0.79, 0.97), respectively. Postvaccination SCR differences with 95% confidence intervals for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria were -11.46% (-16.45, -6.42), 3.13% (-1.44, 7.81), -14.87% (-19.61, -9.98), -5.96% (-10.33, -1.44), respectively. These results meet the predefined success criteria for all eight primary immunogenicity endpoints.

The most frequent local solicited adverse reactions during this study were tenderness and erythema of the injection site, which were reported in 27.9% and 25.8% of QIVc recipients, respectively, and 30.0% and 24.6% of QIV recipients, respectively. The most frequent systemic solicited adverse reactions were irritability and sleepiness, which were reported 27.9% and 26.9% of QIVc recipients, respectively, and 29.6% and 25.5% of QIV recipients, respectively. QIVc recipients had a slightly higher rate of solicited adverse reactions that were Grade 3 or higher compared to QIV recipients, as well as a slightly higher rate of adverse reactions that persisted beyond Day 7 compared to QIV recipients. These differences may be attributed to the higher antigen dose in QIVc compared to QIV for children less than 3 years of age. QIVc recipients and QIV recipients experienced similar rates of unsolicited AEs between Day 1 and Day 29/57. There were apparent imbalances of SAEs among QIVc recipients, with 4 serious events of pneumonia and 3 serious events involving seizures. However, each of these events were assessed as unlikely to be related to QIVc. The overall rate of SAEs was balanced between QIVc recipients and QIV recipients with a rate of 0.9% in each arm of the study. Similarly, the rates of MAAEs and NOCDs were generally balanced between treatment arms.

7. INTEGRATED OVERVIEW OF EFFICACY

Not applicable, only one study was included in this application.

8. INTEGRATED OVERVIEW OF SAFETY

Not applicable, only one study was included in this application.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Section 8 of the package insert complies with the Pregnancy and Label Labelling Rule. The section of the package insert was most recently updated as part of the clinical efficacy supplement STN 125408/329. No revisions of this section were added as part of the clinical efficacy supplement.

9.1.2 Use During Lactation

Data are not available to assess the effects of QIVc in the breastfed infant or on breastmilk production or excretion.

9.1.3 Pediatric Use and PREA Considerations

The purpose of this clinical efficacy supplement is to provide Study V130_10 results to fulfill the PREA postmarketing study requirement for QIVc in children 6 months to through 23 months of age. Study V130_10 was originally designed to demonstrate the

immunologic non-inferiority of QIVc to a U.S.-licensed comparator vaccine in children 6 months through 47 months of age. However, prior to submitting the results of Study V130_10 in this supplement, the Applicant submitted the results of study V130_12, a pediatric efficacy study in children 2 through 17 years of age, in supplement STN 125408/329. Following the review of V130_12, CBER concluded that the results supported the safety and efficacy of QIVc in children 2 years through 3 years of age. As such, the results of V130_12 constituted an assessment for children 2 years through 3 years of age and partially fulfilled PMR #2. The assessment for children 6 months through 23 months of age from V130_10 is intended to fulfill the remainder of PMR #2.

The safety and immunogenicity data from Study V130_10 support granting "traditional" approval, thereby fulfilling the requirements to conduct a postmarketing study to describe the clinical benefit of QIVc in children 6 months through 23 months of age. Therefore, V130_10 constitutes a pediatric assessment to address PREA requirements for children 6 months through 23 months of age. We therefore consider the remainder of PREA postmarketing requirement #2 to be fulfilled based on the results of V130_10.

9.1.4 Immunocompromised Patients

Use of QIVc has not been studied in immunocompromised individuals.

9.1.5 Geriatric Use

QIVc has been evaluated in approximately 660 subjects 65 years and older in previous clinical investigations, and QIVc is currently approved for use in the elderly.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Not applicable.

10. CONCLUSIONS

The safety and immunogenicity data submitted to this efficacy supplement through Study V130_10 support granting "traditional" approval to QIVc for children 6 months through 23 months of age for the indication of active immunization for the prevention of influenza disease caused by influenza A subtypes and type B viruses contained in the vaccine. Therefore, the results of Study V130_10 constitute a pediatric assessment which satisfies PREA postmarketing requirement #2.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

Table 41. Risk-Benefit Assessment of QIVc in Persons 6 Months Through 23 Months of Age

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Influenza typically causes annual seasonal epidemics and can sometimes cause pandemics. • Disease is most severe (i.e., the highest rates of hospitalization and mortality) in the elderly, young children, and individuals with underlying medical comorbidities that place them at increased risk of complications. • Influenza typically infects 5-20% of the population each year. Infections result in a wide range of severity, with between 140,000 and 810,000 hospitalizations and between 12,000 and 61,000 deaths annually in the United States.	• Considerable morbidity and mortality is associated with yearly influenza epidemics. Influenza vaccines are the most effective method of preventing morbidity and mortality associated with influenza infection. • The CDC estimates that since 2010, influenza-related hospitalizations among children younger than 5 years of age have ranged from 7,000 to 26,000 in the United States.
Unmet Medical Need	• The majority of inactivated influenza vaccines, and one live-attenuated vaccine, licensed in the United States are produced in embryonated hen eggs. The use of eggs in the manufacture of these vaccines results in a reliance on the national egg supply, long production timelines, limited capacity to scale up production of vaccines in the event of an emergency, and inclusion of potentially allergenic egg proteins in vaccines. • Antiviral agents including oseltamivir, zanamivir, peramivir, and baloxavir marboxil are licensed for the treatment and prevention of influenza infections; however, their utility is limited by the need for early intervention after influenza infection, as well as emergence of antiviral resistance. One study reported that oseltamivir-resistant influenza A viruses were isolated from 9 (18%) of 50 Japanese children who received antiviral therapy with oseltamivir. Antiviral resistant strains of influenza are transmissible from person to person.	• QIVc is the first cell-derived influenza vaccine to be licensed in the United States. • QIVc is the only non-egg based influenza vaccine that is licensed for children. • QIVc is manufactured in MDCK cells instead of eggs, and as a result, it is easier to increase the scale of vaccine production. • QIVc contains unmeasurable amounts of egg proteins, and therefore may be appropriate for use in children with egg allergies.
Clinical Benefit	• Study V130_10 demonstrated the non-inferiority of the immunogenicity of QIVc compared to a U.S.-licensed comparator quadrivalent influenza vaccine. 1787 subjects received either study vaccine and had valid serologic samples for immunogenicity analyses: 1169 subjects received QIVc and 618 subjects received the U.S.-licensed comparator vaccine. The pre-defined success criteria were met for all eight immunogenicity endpoints. • Certain racial groups including Asians, Native Hawaiians/Pacific Islanders, and American Indians/Alaska Natives were not enrolled in large enough to form a meaningful comparison to other racial groups, and therefore subgroup analyses of safety and immunogenicity specific to these racial groups were very limited.	• Evidence of clinical benefit was demonstrated in this noninferiority immunogenicity study.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The most substantial risks of vaccination with QIVc includes local and systemic adverse reactions, including severe events. The most frequent solicited adverse reactions in V130_10 were injection site pain or tenderness, irritability, and sleepiness. Postmarketing safety monitoring has identified the following potential risks associated with vaccination: allergic or immediate hypersensitivity reactions, including anaphylactic shock, syncope, presyncope, paresthesias, injection site reactions including extensive swelling of the injected limb, generalized skin reactions including pruritus, urticaria or other non-specific rashes. • The serious adverse events, including deaths, that occurred during V130_10 were considered unrelated to administration of the study vaccine by the Applicant and by this reviewer. In general, the occurrence of SAEs, NOCDs, and MAAEs were comparable between vaccination groups. • There appeared to be a proportionately larger number of serious cases of pneumonia and seizures among QIVc recipients; however, these events were considered unlikely to be related to administration of QIVc.	• The most common adverse reactions were mild to moderate in severity and were self-limited.
Risk Management	• The most frequently reported adverse events related to QIVc were reactions at the injection site that were mild and resolved within several days. Solicited local and systemic adverse events will be described in the package insert.	• The risks of QIVc are adequately addressed in the package insert. • Postmarketing safety data is being collected for QIVc following licensure for children 2 years through 17 years of age. • The proposed risk management plan includes routine pharmacovigilance with adverse event reporting as required under 21 CFR 600.80.

11.2 Risk-Benefit Summary and Assessment

Per the Applicant, QIVc's cell culture-based manufacturing platforms confers several advantages, including increased manufacturing control and surge capacity as well as the potential to address reduced effectiveness against circulating A/H3N2 strains of virus as a result of egg-adaptive mutations in the HA protein.

The data submitted in this BLA supplement establish the safety and immunogenicity of QIVc in children 6 months through 47 months of age. Although the database was adequate for the assessment of safety, a larger safety database may elucidate the risks, if any, for imbalances observed, and imbalances of rare events or events for which the effect size may be small.

The risks associated with vaccination with QIVc observed in V130_10 include mostly mild to moderate and self-limited local and systemic reactogenicity, and infrequent severe reactogenicity. The overall rate of adverse reactions was balanced between the older and younger age groups in V130_10, and the rate of adverse reactions was comparable to the U.S.-licensed QIV comparator vaccine. The overall risk of vaccination appears minimal based on the submitted safety data. The immunogenicity data support clinical benefit and a favorable risk-benefit determination.

11.3 Discussion of Regulatory Options

The Applicant is seeking full approval of QIVc for use in children 6 months through 17 years of age. The indication remains unchanged: *For active immunization for the prevention of influenza disease caused by influenza virus subtypes A and B contained in the vaccine.*

The immunogenicity and non-inferiority analyses follow FDA guidance for data to support effectiveness and "traditional approval" of seasonal influenza vaccines.

11.4 Recommendations on Regulatory Actions

After reviewing the V130_10 clinical study report, this clinical reviewer agrees that the safety and immunogenicity of QIVc in children 6 months through 47 months of age supports granting "traditional" approval for QIVc to extend the indication for use down to individuals 6 months of age and older. Submission of the data from V130_10 fulfills PREA postmarketing requirement #2.

11.5 Labeling Review and Recommendations

With this clinical efficacy supplement, the information about the safety and immunogenicity of QIVc in children 6 months through 47 months was added to the QIVc label. Section 6.1 was revised to describe the study design and safety findings for Study V130_10 ("Study 1" in the label). Table 9 of Section 14.4 was revised to describe the immunogenicity results from V130_10, with an added footnote that includes the immunogenicity results for strain A/H3N2 using HAI assay.

11.6 Recommendations on Postmarketing Actions

The Applicant intends to follow the current routine pharmacovigilance plan, as no new safety signals were identified during V130_10. There are no additional PMRs or postmarketing commitments related to this submission.