BLA Clinical Review Memorandum

Application Type	Efficacy Supplement
STN	125408.329
CBER Received Date	31 March 2020
PDUFA Goal Date	29 January 2021
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	No
Reviewer Name	Anuja Rastogi, MD MHS
Review Completion Date / Stamped Date	
Supervisory Concurrence	Lucia Lee, MD CRB1 Team Leader Maria Allende, MD CRB1 Branch Chief
Applicant	Seqirus, Inc.
Established Name	Influenza Vaccine
Trade Name	Flucelvax Quadrivalent
Pharmacologic Class	Vaccine
Formulation	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 and Route of Administration	Suspension; intramuscular injection
Dosing Regimen	2 through 8 years of age: one dose, or, two doses administered at least 4 weeks apart, depending upon prior influenza immunization; 9 years of age and older: one dose
Indication(s) and Intended Population(s)	Active immunization in persons 2 years of age and older for the prevention of influenza disease caused by influenza A subtypes and type B viruses contained in the vaccine
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	Adverse event
BLA	Biologics license application
CFR	Code of Federal Regulations
CMC	Chemistry, manufacturing, and controls
CSR	Complete study report
PeRC	Pediatric Review Committee (CDER)
PMC	Post marketing commitment
PMR	Post marketing requirement
PREA	Pediatric Research Equity Act
PVP	pharmacovigilance plan
SAE	Serious Adverse Event
USPI	US package insert

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 initially approved for use in in persons 4 years of age and older on 23 May 2016 [STN 125408/127], with accelerated approval (21 CFR 601.40-46) granted for ages 4 years to <18 years of age based on the demonstration of noninferior immunogenicity and comparable safety to Flucelvax® (trivalent) vaccine based on data from Study V130_03 that included 2,333 children (4years to <18years). With this clinical efficacy supplemental biological license application [sBLA], the applicant provides the study report for V130_12 to support extended use of QIVc to children as young as 2 years of age and to satify the accelerated approval requirements for children 4 to <18 years of age. The indication, active immunization for the prevention of influenza disease caused by the Influenza A subtypes and type B viruses contained in the vaccine, remained unchanged.

Efficacy:
Study V130_12, "A Phase III/IV, Stratified, Randomized, Observer Blind, Multicenter Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of a Cell-Based Quadrivalent Subunit Influenza Virus Vaccine Compared to Non-Influenza Comparator Vaccine in Subjects ≥ 2 years to <18 years of age," was designed to include a non-influenza comparator (Meningococcal Group ACWY Conjugate Vaccine (GSK, Menveo®)) to allow an estimation of absolute vaccine efficacy (aVE) of QIVc in preventing influenza in pediatric participants. The primary efficacy objective was to demonstrate aVE of QIVc relative to the comparator to prevent the 1st occurrence of RT-PCR or culture-confirmed influenza, due to any influenza Type A and B strain in participants 2 years to < 18 years of age, and in children 3 years to <18 years of age as a co-primary efficacy objective. An influenza case was defined as RT-PCR-confirmed or culture-confirmed influenza that met the Centers for Disease Control and Prevention (CDC) criteria for influenza-like illness (ILI) modified for young children (fever, along with any of the following symptoms: cough, sore throat, nasal congestion, or rhinorrhea). There were a total of 2444 ILI cases (1193 QIVc group, 1251 comparator group) reported in 1685 participants (791 QIVc participants, 894 comparator participants). Efficacy was demonstrated in 2 to <18 years of age if the lower limit (LL) of the 2-sided 95% confidence interval (CI) for aVE was above 20% (primary objective) and in 3 to <18 years of age if the LL of the 2-sided 95% CI for aVE was above 30% (co-primary objective). The lower bound of the 2-sided 95% CI for vaccine efficacy

was 45.67% for QIVc in participants 2 through 17 years (<18 years) and 44.8% for QIVc in participants 3 through 17 years (<18 years), therefore both primary objectives were met. The cultured confirmed aVE estimate for antigenically matched strains in all participants (2 through <18 years) was highest against strain A/H1N1 (82% [95 % CI: 69.95%, 89.33]) and B/Yamagata (51.9% [32.3, 65.28]). By influenza season/hemisphere, the aVE against all strains across seasons/hemispheres, was greatest in Season 1-SH 2017 (56.68% [44.18, 66.22]) and Season 3-NH 2018-2019 (59.49%, [41.03, 72.18), and the lowest aVE observed following Season 2-NH 2017-2018(44.16 [19.93, 61.05]. The clinical endpoint efficacy data met the predefined success criteria and support the effectiveness of Flucelvax for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine in persons 4 years through <18 years and children 2 years through <4 years of age.

Safety:
No new safety concerns were identified following the review of safety data from study V130_12. For participants 2 years through 8 years, the most frequent solicited adverse reactions (ARs) were injection site tenderness and pain, reported in ~27 - 28% in the QIVc group compared to 25% and 20% in the comparator group, respectively. In addition, headache, irritability, and loss of appetite were reported in 13.8% vs 11.8%, 13.8% vs 10.8%, and 10.6% vs 8.0% of QIVc vs comparator recipients, respectively. The rates of Grade 3 (severe) ARs were comparable across groups, and were generally <1% in the QIVc group.

For participants 9 years through 17 years, the most frequent solicited reaction was injection site pain, reported in ~22% (<1% Grade 3) in the QIVc group compared to 18% (1% Grade 3) in the comparator group. In addition, headache and loss of appetite were reported in 18.1% vs 17.4% and 8.5% vs 7.5% of QIVc vs comparator recipients, respectively. Irritability was only assessed in participants 2 through <6 years. The rates of unsolicited non-serious AE following study vaccinations were comparable across study groups, including those graded severe in intensity (0.5% in both groups). Across groups the rates of SAEs were ~1%, NOCDs were $\leq$ 0.5%, and AEs concluded by the study investigator to be at least possibly related were ~4%, while MAEEs were lower in the QIVc group (27%) than the comparator group (30%). There were no deaths in QIVc recipients, one death in a comparator vaccine recipient, and no SAEs that were considered by the study investigator or this reviewer to be related to study vaccinations.

Pediatric Assessment and Pediatric Research Equity Act (PREA)
The study report for Study V130_12 includes data in children 2 years through 17 years of age. The study was originally designed to evaluate the safety and efficacy of QIVc only in children 4 years through 17 years of age to fufill requirements for accelerated approval in this age group. However, a protocol amendment was submitted to the IND, reviewed and concurred by DVRPA to include children 2 through 3 years (<4 years); the applicant submitted the amended protocol to align with other regulatory agencies. The study population included 432 randomized participants 2 years through 3 years of age (9.6% of total participants), including 212 QIVc recipients and 220 placebo recipients.

According to the agreed Pediatric Study Plan, a safety and immunogenicity study, V130_10, to evaluate QIVc in children 6 months through 3 years (<4 years) was intended to fulfill the PREA requirements for children 2 to <4 years of age. In this reviewer's opinion, the safety and efficacy data from V130_12 constituted a pediatric assessment in children 2 years through <4 years with a sufficient number of evaluable QIVc recipients in this pediatric age cohort, as required under the Pediatric Research Equity Act (PREA). We therefore consider PREA PMR #2 to be partially fulfilled (for the age group 2 years to < 4 years of age) based on the study V130 12 results. This pediatric assessment in children 2 years through <4 years was presented to PeRC on January 19,

2021. The assessment for ages 6 months to <2 years, based on study V130_10 results, will be presented to PeRC under STN 125408/(b) (4).

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

When evaluated by age sub-cohorts, aVE against all strains in participants 2 through 3 years of age was 62.66% [38.06, 77.49]; participants 2 through 8 years of age was 50.51% [38.43, 60.22]; and in participants 9 years through 17 years was 61.85% [47.37, 72.34]. However, by age sub-cohorts, the aVE against A/H3N2 strain was 48.71 [-20.73, 78.21], 32.82% [-0.96, 55.30], and 53.93% [22.66, 72.55], respectively for participants 2 through 3 years, 2 through 8 years, and 9 through 17 years; the study was not powered to evaluate vaccine-strain specific aVE by subgroup. There was no difference observed in aVE estimates based on sex or between White and Asian participants. There were too few participants in other racial groups (<1.0%) to estimate vaccine efficacy, though it is not anticipated that VE would differ based on racial/ethnic origin. There were no differences observed in VE based on prior influenza vaccination history.

The reported rates of unsolicited AEs were higher in participants 2 through 8 years (37.7% QIVc vs 39.5% comparator) than participants 9 through 17 years (18.1% QIVc vs 16.0% comparator), and most events were graded mild/moderate in severity. The most frequently reported events by PT were upper respiratory tract infections and rhinitis. Events considered related to vaccination were also higher in the younger age cohort (5.9% QIVc vs 4.4%; mainly due to higher rate of injection site erythema) compared to the older age cohort (2.6% QIVc, vs 3.5% comparator). The rates of SAEs and NOCD in both age sub-cohorts were low across groups. There was one death in the 2 to 8 years age sub-cohort in the comparator group, an 8-year-old female with diabetic ketoacidosis and cerebral edema on Day 220 of the study, considered not related to study vaccination by the study investigator and this reviewer. There were no differences observed in the rates of unsolicited AEs based on race or sex. The rates of unsolicited AEs were higher in participants not previously vaccinated (43.9% QIVc vs 45.6% comparator) than in participants previously vaccinated (19.8% QIVc vs 18.8% comparator).

1.2 Patient Experience Data

Patient experience data were not submitted as part of this application.

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, deaths due to influenza illness in the United States ranged from 12,000-61,000. The rates of infection are highest among children, but serious illness and death are reported more frequently among persons older than 65 years of age and persons of any age who have chronic underlying medical conditions (as defined by the ACIP) that place them at increased risk of complications. Influenza vaccination is the primary method for preventing influenza illness and its severe complications. In certain circumstances, antiviral medication can be an important adjunct to the vaccine for prevention and control of influenza.

The Advisory Committee on Immunization Practices (ACIP) recommends routine influenza vaccination annually for all persons six months of age and older. The ACIP recommendations also support additional efforts or programs to focus on vaccination of persons at higher risk for influenza-related complications, which includes but is not limited to persons greater than or

equal to 50 years of age, persons with chronic medical conditions, children aged 6 months of age and older, and health care workers.

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

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

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

2.3 Safety and Efficacy of Pharmacologically Related Products

There are currently 18 seasonal influenza polyvalent vaccines (10 trivalent, 8 quadrivalent,) that are licensed in the U.S. Two of the vaccines are live, attenuated; two are cell-based, inactivated vaccines; 14 are egg-based inactivated vaccines. Each of these licensed influenza vaccines have the indication for the prevention of influenza infection for the strains contained in the vaccine and each has an acceptable safety profile.

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

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

Flucelvax trivalent (TIVc) formulation has been licensed in the U.S. since 2012 and Flucelvax Quadrivalent (QIVc) was licensed for use in 2016. Marketing authorization was granted in Europe in 2018, in Canada in 2019, and in Brazil in 2020. Routine pharmacovigilance has not revealed any new safety signals.

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

Initial QIVc regulatory submissions included data from two QIVc Phase 3 immunogenicity and safety clinical studies, one study in adults aged 18 years and above (Study V130_01, NCT01992094, QIVc exposed: 1334 participants) and one study in children 4 to < 18 years of age (Study V130_03, NCT01992107, QIVc exposed 1159). Licensure of QIVc was supported by 12 TIVc randomized controlled studies in adults and children 3 years of age and older.

FDA granted accelerated approval (AA) for use of Flucelvax® Quadrivalent in children 4 years to <18 years of age on 23 May 2016. The clinical data supported “traditional” approval for adults 18 years and older. Study V130_12 was designed as an efficacy, immunogenicity, and safety Phase 3 study conducted in accordance with requirements for AA to confirm the clinical benefit

of QIVc in children ≥4 to <18 years of age. The study design of V130_12 was revised several times under the IND and the final protocol was version 5, dated 13December 2018. Important revisions included with the final protocol:

- Age range extended to included participants ≥2 years (originally ≥4 years)
- Addition of primary objective: vaccine efficacy in children 2 years through <18 years, with co-primary objective: VE in children 3 years through <18 years
- The # of influenza confirmed cases needed to proceed to final analyses was increased from 144 to 381 to maintain adequate study power
- Assessment of (b) (4) responses was added as an exploratory objective because emerging H3N2 viruses lost HA-mediated hemagglutination. The QIVc H3N2 component is produced from a cell culture-derived vaccine virus (CVV) which maintains circulating virus characteristics such as HA-mediated hemagglutination loss. Therefore, the hemagglutination inhibition (HI) assay with the H3N2 whole virus cannot be used to evaluate H3N2 immunogenicity. However, H3N2 is a key disease-causing subtype and measuring responses against it would be of value to support the choice of immunogenicity endpoints (inferred efficacy) in study V130_10.

The applicant's rationale to include children ≥2 years of age (rather than just ≥4 years) was to further evaluate QIVc in a broader age range and to support submissions in various global regions.

The sBLA with data from Study V130_12 was submitted on 31March 2020 and was filed on 30May 2020. In this study 2258 participants were exposed to QIVc, including 212 participants 2 through <4 years of age. The safety and clinical efficacy data support granting "traditional" approval of Flucelvax QIVc in children 4 years through 17 years of age (<18 years). The indication is unchanged. The safety and clinical endpoint efficacy data in children 2 years through <4 years support the safety and effectiveness of QIVc in this age group, and as such, constitute a pediatric assessment in children 2 to <4 years of age, which was presented to the Pediatric Research Committee (PeRC) on 19January 2021. The committee agreed with the DVRPA's conclusion.

The sponsor submitted multiple amendments with revised labels to the sBLA during the review cycle. The package insert is appropriately labeled for the pediatric population 2 to <18 years of age.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission of this efficacy sBLA 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_12 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 21CFR 50.25.

The final protocol was version 5.0, dated 13Dec 2018. The informed consent form was reviewed and approved by a national, regional, or investigational center-IEC, or Institutional Review Board-IRB and the final version ICF was version 5, dated 25June 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. IRB approvals for study sites/principal investigators were provided by multiple regional IRBs in Australia, Estonia, Poland, Finland, Philippines, Thailand, Lithuania, and Spain.

3.3 Financial Disclosures

Covered clinical study (name and/or number): V130_12		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 39		
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

This sBLA did not include new CMC information.

4.2 Assay Validation

This sBLA did not include new assay validation information.

4.3 Nonclinical Pharmacology/Toxicology

This sBLA did not include new pharmacology/toxicology information

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Vaccination against influenza results in hemagglutination inhibition antibody titers. Specific levels of antibody have been correlated with protection from influenza illness. In some studies, HAI antibody titers of ≥ 1:40 have been associated with protection from influenza illness in up to 50% of subjects.

4.4.2 Human Pharmacodynamics (PD)

Not applicable

4.4.3 Human Pharmacokinetics (PK)

Not applicable

4.5 Statistical

The CBER statistical reviewer (Dr Elizabeth Teeple) verified the primary efficacy analyses in the study report as accurate. There were no major statistical issues related to the submission.

4.6 Pharmacovigilance

The applicant's current pharmacovigilance plan (PVP) is dated March 25,2020. Important identified risks include anaphylaxis, and important potential risks include convulsion, Guillain-Barre Syndrome, demyelination, vasculitis, and immune thrombocytopenia purpura, which will be followed with routine PVP. Based on review of the data in this clinical efficacy supplement, the CBER PVP reviewer (Dr Christopher Jason) concluded that the current routine PVP plan is adequate. The pregnancy registry study (V130_11OB) for QIVc has been completed, and the final study report has not been submitted to date.

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_12 to support the efficacy, safety and immunogenicity (subset of participants) of QIVc in children 2 years through 17 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, M1.14.1, M1.16.1, M2.2, M2.5, M2.7, M5.3.5.1
- Amendment 1: M1.11.3, M5.3.5.1
- Amendment 2: M1.11.3, M
- Amendment 3: M1.11.3
- Amendment 4: M1.11.3
- Amendment 5: M1.11.3
- Amendment 6: M1.11.3

- Amendment 7: M1.11.3
- Amendment 8: M1.14.1
- Amendment 9: M1.14.1

5.3 Table 1: Overview of Clinical Trials

Study Number	**Country Influenza Season-Hemisphere**	**Description (relevance to US licensure)**	**Population**	**Study Groups: #Exposed**
Pivotal Study V130_12	Australia Estonia Finland Lithuania Philippines Poland Spain Thailand 2017 SH 2017 NH 2018 NH 2018-2019 NH	Phase 3 Efficacy Safety Immunogenicity	Healthy participants 2 years through 17 years (<18y)	QIVc: 2258 Non-influenza comparator: 2255 (Menveo/saline placebo)

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

An Advisory Committee meeting was not convened during the review of this sBLA.

5.4.2 External Consults/Collaborations

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

5.5 Literature Reviewed (if applicable)

CDC (US Centers for Disease Control and Prevention). Seasonal influenza activity surveillance reports: 2010-2020. Available at: https://www.cdc.gov/flu/about/burden/index.html#:~:text=While%20the%20impact%20of%20flu,61%2C000%20deaths%20annually%20since%202010
(accessed February 1, 2021)

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1 (V130_12)

NCT# 03165617
A Phase III/IV, Stratified, Randomized, Observer Blind, Multicenter Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of a Cell-Based Quadrivalent Subunit Influenza Virus Vaccine Compared to Non-Influenza Comparator Vaccine in Participants ≥2 Years to <18 Years of Age

Study Overview: Following a Biologics License Application (BLA) in April 2015, marketing authorization of QIVc for the prevention of seasonal influenza in both adult and pediatric participants (≥4 years of age) was approved by the FDA in May 2016 (trade name Flucelvax® Quadrivalent). Study V130_12 was initially designed to fulfull the US regulatory (post-marketing) requirement to verify and describe the clinical benefit of QIVc in children 4 to <18 years of age. Children ≥2 years of age were enrolled in this study to comply with requirements for other regulatory agencies.

6.1.1 Objectives

The study objectives, endpoints, and statistical success criteria, if applicable are described below.

Primary Efficacy Objectives:

1. To demonstrate the absolute vaccine efficacy (aVE) of QIVc versus a non-influenza comparator determined by the first occurrence of RT-PCR- or culture-confirmed influenza, due to any influenza Type A and B strain in participants ≥2 to <18 years of age
2. To demonstrate the aVE of QIVc versus a non-influenza comparator determined by the first occurrence of RT-PCR- or culture-confirmed influenza, due to any influenza Type A and B strain in participants ≥3 to <18 years of age.

   Primary Endpoint:
   The time from the last study vaccination to the onset of the first occurrence of either RT-PCR- or culture-confirmed influenza (time-to-event analyses) due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season

   Criteria for Success:
   1. Primary Objective #1: The efficacy of QIVc was demonstrated in participants 2 to <18 years of age if the lower limit (LL) of the 2-sided confidence interval (CI) of the VE estimate with at least 95% coverage in multiple sequential hypothesis testing was above 20%
   2. Co-Primary Objective #2: The efficacy of the QIVc was demonstrated in participants 3 to <18 years of age if the LL of the 2-sided CI of the VE estimate, with at least 95% CI coverage in multiple sequential hypothesis testing was above 30%.

Secondary Efficacy Objectives:
The following objective was evaluated in the age cohorts: 2 to <9 years of age, 4 to <18 years of age, and 9 to <18 years of age:

1. To demonstrate aVE of QIVc versus a non-influenza comparator determined by the first occurrence of RT-PCR- or culture-confirmed influenza due to any influenza Type A and B strain.

   Endpoint #1:
   The time from the last study vaccination to the onset of the first occurrence of either RT-PCR- or culture-confirmed influenza due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season.

The following objectives were evaluated in the age cohorts: 2 to <18 years of age, 4 to

<18 years of age, 2 to <9 years of age, and 9 to <18 years of age:

2. To demonstrate aVE of QIVc versus a non-influenza comparator determined by the first occurrence of RT-PCR-confirmed influenza due to any influenza Type A and B strain.
   Endpoint #2:
   The time from the last study vaccination to the onset of the first occurrence of RT-PCR-confirmed influenza due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season.

3. To demonstrate aVE of QIVc versus a non-influenza comparator determined by the first occurrence of culture-confirmed influenza due to any influenza Type A and B strain.
   Endpoint #3:
   The time from the last study vaccination to the onset of the first occurrence of culture-confirmed influenza due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season.

4. To demonstrate aVE of QIVc versus a non-influenza comparator determined by the first occurrence of culture-confirmed influenza caused by influenza strains antigenically matched to the strains selected for the seasonal vaccine.
   Endpoint #4:
   The time from the last study vaccination to the onset of the first occurrence of culture-confirmed influenza due to influenza Type A or B strain antigenically matched to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season.

Secondary Immunogenicity Objective
To characterize the immunogenicity of QIVc by HI assay 3 weeks after the last vaccination in a subset of participants in the age cohort 2 to <9 years of age.

Endpoints:
The immunogenicity of study vaccines was assessed 21 days after the last vaccine administration by measuring the HI assay to the 4 viral strains included in the vaccines.

1. The measures for assessing immunogenicity as determined by HI were as follows: HI geometric mean titers (GMTs) on Day 1 (all participants), Day 22 (all "previously vaccinated" participants receiving a single vaccine dose) or Days 29 and 50 (all "not previously vaccinated" participants receiving 2 doses) for all 4 influenza strains.
2. Percentage of participants achieving seroconversion (SC) (defined as: either a pre-vaccination HI titer <1:10 and a postvaccination HI titer ≥1:40 or a pre-vaccination HI titer ≥1:10 and a ≥4-fold increase in postvaccination HI titer) on Day 22 (all "previously vaccinated" participants receiving a single vaccine dose) or Days 29 and 50 (all "not previously vaccinated" participants receiving 2 doses) for all 4 influenza strains.
3. HI geometric mean ratio (GMR)1 of Day 22/Day 1 (all "previously vaccinated" participants receiving a single vaccine dose) or Day 29/Day 1 and Day 50/Day 1 (all "not previously vaccinated" participants receiving 2 doses) for all 4 influenza strains.
4. Percentage of participants with an HI titer ≥1:40 on Day 22 (all "previously vaccinated" participants receiving a single vaccine dose) or Days 29 and 50 (all "not previously vaccinated" participants receiving 2 doses) for all 4 influenza strains.

Secondary Safety Objective

To assess safety and tolerability of QIVc

Endpoints:

1. Percentage of participants with solicited local and systemic adverse events (AEs) for 7 days after vaccination on Day 1 (for "previously vaccinated" participants) or for 7 days after vaccination on Day 1 and Day 29 (for "not previously vaccinated" participants) in the QIVc group and the non-influenza comparator vaccine group.
2. Percentage of participants with unsolicited AEs assessed from Day 1 to Day 22 (for "previously vaccinated" participants) or from Day 1 to Day 50 (for "not previously vaccinated" participants) in the QIVc group and the non-influenza comparator vaccine group.
3. Percentage of participants with SAEs, AEs leading to withdrawal from vaccination and/or the study, ILIs, and New Onset of Chronic Diseases (NOCDs) reported during the subject's entire participation in the study (ie, from Day 1 to Day 181 [for "previously vaccinated" participants] or from Day 1 to Day 209 [for "not previously vaccinated" participants]), or until the end of influenza season, whichever was longer, and all medications associated with these events.
4. Percentage of participants with medically-attended AEs within 30 days after the first occurrence of ILI.

Exploratory Efficacy Objectives

The following objective was evaluated in the 2 to <18 years of age cohort:

1. To further characterize the efficacy of QIVc, with specific attention for all-cause mortality, all-cause pneumonia, and all-cause otitis media.

   Endpoints:

   - Number of deaths as derived from SAE forms
   - Number of participants with pneumonia as derived from AE forms
   - Number of participants with physician confirmed otitis media as derived from AE forms

The following objective was to be evaluated in the 2 to <18 years of age cohort after completion of the CSR:

2. To describe the aVE of QIVc versus a non-influenza comparator determined by the occurrence of culture-confirmed illness caused by influenza H3N2 virus strains antigenically matched to the influenza H3N2 A/Singapore/GP2050/2015 (cell seed) strain.

Endpoints:

The time from the last study vaccination to the onset of the first occurrence of culture-confirmed influenza, due to any influenza H3N2 virus strains antigenically matched to the influenza H3N2 A/Singapore/GP2050/2015 (cell seed) strain, that occurred at >14 days after the last vaccination until the end of the influenza season.

Exploratory Immunogenicity Objective

To further characterize the immune response in a subset of participants in the age cohort 2 to <9 years of age, using other assays, such as MN.

Endpoint:

In the event of additional immunogenicity analyses, such as MN, the immune response was characterized in a similar manner as described in the secondary immunogenicity endpoints.

6.1.2 Design Overview

V130_12 was a randomized, observer-blinded, multicenter study to evaluate the efficacy, safety and immunogenicity of Flucelvax Quadrivalent (QIVc) compared to a non-influenza comparator vaccine in healthy male and females participants 2 to <18 year of age. The study

was case-driven and conducted over 3 influenza seasons, with the total number of recruited participants dependent on the number of laboratory-confirmed influenza cases reported via active surveillance through the end of each season.

Approximately equal numbers of participants ages ≥2 years to ≤9 years and ≥9 years to <18 year were to receive either QIVc or MenACWY. Participants <9 years of age who had not received a previous influenza vaccination received two doses of Flucelvax Quadrivalent, separated by one month OR one dose of MenACWY, followed by a dose of normal saline one month later. Participants between 2 to <9 yo were further stratified as either previously vaccinated (any subject 9 to <18 yo, any participants 2 to <9 yo who had received ≥2 doses of seasonal influenza vaccine before or during the last influenza season) or not previously vaccinated (any subject 2 to <9 yo who had not received ≥2 doses of seasonal influenza vaccine before or during the last influenza season).

The study included 1 or 2 vaccination visits (Day 1, Day 29) depending on prior influenza vaccination history, followed by a reminder phone call (Day 3, Day 31) two days after a vaccination visit, and a clinic visit (Day 29, Day 50) 3 weeks after a vaccination visit. The study follow-up period was through 6 months after the last dose or the end of the influenza season, whichever was longer, and included 2 safety phone calls, on Day 91 & Day 181 for previously vaccinated participants, or Day 120 & Day 209 for not previously vaccinated participants. Participants with influenza like illness (ILI) symptoms required a clinic or home visit for collection of a nasopharyngeal swab within 3 to 6 days after symptom onset, followed by a safety follow-up call 30 days after symptom onset.

Following randomization on Day 1, all participants received a 0.5mL dose of study vaccine (QIVc or MenACWY) administered intramuscularly in the deltoid muscle, preferably of the non-dominant arm. For participants who were not previously vaccinated, a 2nd dose was administered on Day 29. For participants randomized to the QIVc group, the 2nd dose was QIVc, and for participants randomized to the non-influenza comparator group, the 2nd dose was placebo (saline for injection).

6.1.3 Population

Study participants were healthy children/adolescents 2 to <18 years of age for whom consent was obtained from parents/legal guardian or assent from the child/adolescent, as applicable. Participants were excluded from study participation for any of the following:

- Fever within 3 days prior to vaccination (oral temp ≥100.4F)
- History of anaphylaxis of serious reaction after administration of any vaccine or hypersensitivity to any of the vaccine components, or any contraindication listed in the USPI of the comparator vaccine
- History of Guillain-Barre syndrome or other demyelinating diseases
- Female participants of children bearing potential and were sexually active had to agree to use appropriate birth control methods as defined in the study protocol
- Pregnant or breast feeding female
- Participants or parent/guardian who are not able to comprehend the required study procedures
- Prior receipt of meningococcal ACWY vaccination that conflicted with national recommendations or local practices for the timing of the primary or the booster vaccinations
- Prior receipt of influenza vaccination or documented influenza disease within the previous 6 months
- Known or suspected congenital or acquired immunodeficiency, receipt of immunosuppressive therapy (chemotherapy, radiation therapy), within the preceding 6

months; or systemic corticosteroid therapy (prednisone or systemic corticosteroid therapy) at any dose for more than 2 consecutive weeks within the past 3 months. (Topical, inhaled, and intranasal corticosteroid therapy and intra-articular 1 dose within 30 days permitted)

- Immunoglobulin and/or any blood product within 30 days prior to 1st study visit, or administration was planned during the study
- Participation in any clinical study with another investigational product within 30 days prior to 1st study visit or intended to participate in another clinical study at any time during the conduct of this study.
- Medical conditions/treatment contraindicating intramuscular vaccination
- Evidence or history within previous 12 months of drug or alcohol abuse
- Study personnel or immediate family members
- Participation in this study in the prior season
- Any condition that may have interfered with evaluation of the study objectives of the safety of the subject

Criteria for Delay of Vaccination:
In the following circumstances, a subject may be eligible for participation after the appropriate window for delay of vaccination has passed and eligibility criteria was reassessed and confirmed as eligible:

- Transient clinical circumstances which would warrant delay of vaccination (body temperature elevation ≥100.4F) within 3 days prior to intended study vaccination)
- Use of antipyretic/analgesic medications within 24 hours prior vaccination

Criteria for Receipt of 2nd Study Vaccination for Participants 'Not Previously Vaccinated':
If participants met any of the original exclusion criteria (except those that were transient clinical circumstances) or any criteria listed below, they could not receive additional vaccinations, but were encouraged to continue study participation:

Participants who experienced any SAE judged to be related to study vaccine including hypersensitivity reactions
Participants who developed any new condition which, in the opinion of the investigator, might pose additional risks if he/she continued to participate in the study

Discontinuation of Participants:
Participants were discontinued/withdrawn from the study for the following reasons:

Adverse Events
Death
Withdrawal of consent/assent
Lost to follow-up
Administration reason
Protocol deviation
Other

6.1.4 Study Treatments or Agents Mandated by the Protocol

Study participants received a 0.5mL intramuscular dose of either QIVc or MenACWY. Participants who were not previously vaccinated, received a 2nd 0.5mL dose of QIVc or placebo-normal saline for injection on Day 29.

*QIVc Study Vaccine*s:
Each QIVc vaccine across the 3 influenza seasons included a total 60 ug of hemagglutinin (HA)-15 μg HA of each of the 2 influenza type A strains & each of the 2 influenza type B strains.

Vaccine composition by season:
Season 1 [Southern Hemisphere 2017]: Lot# 192679, Expiry date 01/2018

- Strain Type A/Singapore/GP1908/2015 IVR 180 (H1N1)
- Strain Type A/HongKong/4801/2014 (H3N2)
- Strain Type B/Utah/9/2014 (B Yamagata)
- Strain Type B/HongKong/259/2010 (B Victoria)

Season 2 [Northern Hemisphere 2017-2018]: Lot# 195215, Expiry date 4/2018

- Strain Type A/Singapore/GP1908/2015 IVR-180 (H1N1) Strain Type A/ Singapore/ GP2050/2015 (H3N2)
- Strain Type B/Utah/9/2014 (B Yamagata)
- Strain Type B/HongKong/259/2010 (B Victoria)

Season 3 [Northern Hemisphere 2018-2019]: Lot# 252661, Expiry date 5//2019

- Strain Type A/Singapore/GP1908/2015 IVR-180 (H1N1) Strain Type A/North Carolina 04/2016 (H3N2)
- Strain Type B/Singapore/INFTT-16-06 10/2016 (B Yamagata)
- Strain Type B/Iowa/06/2017 (B Victoria)

Other components:
Buffer M (PBS) (b) (4)

Water for injection-up to 0.5mL

Active Comparator: Meningococcal Group ACWY Conjugate Vaccine:
The following table provides the composition for MenACWY (Menveo®, GSK).

Table 2: Menveo Composition

Name of Ingredient	Unit and/or Percentage Formula (Dose 0.5 mL)
Drug Substances	--
CRM197-MenA conjugate	10 µg MenA, (b) (4) µg CRM197
CRM197-MenC conjugate	5 µg MenC, (b) (4) µg CRM197
CRM197-MenW conjugate	5 µg MenW, (b) (4) µg CRM197
CRM197-MenY conjugate	5 µg MenY, (b) (4) µg CRM197

MenACWY vaccine Lot# and Expiry Date are provided.
-Season 1 Lot# M16039, Expiry Date 10/2017
-Season 2 Lot# M16106, Expiry Date 07/2018
-Season 3 Lot# M17043, Expiry Date 04/2020

Placebo (Sodium Chloride Injection 0.9% w/v):
Sodium chloride 4.5mg
Water for injection Qs to 0.5mL

Placebo Lot# and Expiry Date:
-Season 1 Lot# 16381013, Expiry Date 08/2019
-Season 2 Lot# 17203011, Expiry Date 02/2020
-Season 3 Lot# 18096011, Expiry Date 02/2021

6.1.5 Directions for Use

QIVc: 0.5mL volume for injection in prefilled syringe administered intramuscularly in the deltoid muscle-nondominant arm

MenACWY: 2 single dose vials that contain lyophilized MenA conjugate vaccine component and liquid MenCWY conjugate vaccine components, respectively. The combined contents of the two vials form a solution. The reconstituted vaccine (0.5mL single dose) was withdrawn from the vial and administered intramuscularly in the deltoid muscle-non-dominant arm.

Placebo (Saline): provided in 5 mL ampoule with a separate 1 mL syringe. Immediately before administration, 0.5 mL of saline for injection was drawn into the syringe.

6.1.6 Sites and Centers

Study 130_12 was conducted at 39 study sites in 8 countries as follows:
-Australia (2 sites)
-Estonia (5 sites)
-Finland (10 sites)
-Lithuania (6 sites)
-Philippines (7 sites)
-Poland (6 sites)
-Spain (1 site)
-Thailand (2 sites)
There were site specific principal investigators in each country.

6.1.7 Surveillance/Monitoring

Safety:
Post-vaccination safety monitoring for immediate AEs occurred for 30 minutes at the study site under medical supervision. The subject's legal guardian/parent or designated persons were instructed on measurements of solicited and local AEs, including body temperature (oral), and on the completion of a subject diary card. Solicited AEs were collected for 7 days after each vaccination dose (all participants: Days 1 through 7; participants receiving 2nd dose: Day 29 through 35).
Solicited AEs were specific to age cohorts: 2 to <6 years and 6 to <18 years (based on age at time of enrollment). The following include the solicited AEs collected by age:

Participants 2 to <6 years:

- Local[1]: injection site induration, erythema, ecchymosis, tenderness
- Systemic: change of eating habits, sleepiness, vomiting, diarrhea, irritability, shivering

Participants 6 to <18 years:

- Local[2]: injection site induration, erythema, ecchymosis, pain

1 For participants <6 years, erythema/ecchymosis/induration measurements: None (0 mm), any (1-9mm, 10-25mm, 26-50mm, >50mm), and severe (>50mm)
2 For participants ≥6 years, erythema/ecchymosis/induration measurements: None (0 mm), Any (1-24 mm, 25-50 mm, 51-100 mm, >100 mm) and Severe (>100 mm).

- Systemic: chills, nausea, generalized myalgia, arthralgia, headache, fatigue, vomiting, diarrhea, loss of appetite

The grading scale for solicited local & systemic AEs for all subject is provided in the table below.

Table 3: Study V130_12 Grading of Solicited Local & Systemic Adverse Events for All Participants

Reaction	**Grade 0 None**	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**
Injection Site Tenderness/Pain	None	No interference with daily activity	Interferes with daily activity	Prevents daily activity
Temperature	<38.0C	≥38.0 - 38.9°C	≥39.0 - 39.9°C	≥40.0C
Change Eating Habits/ Loss of Appetite	None	Eating < normal for 1-2 meals	Missed 1 or 2 feeds/meals	Missed ≥2 feeds/meals
Sleepiness	None	Increased drowsiness	Sleeps through feeds/meals	Sleeps most of the time and
Vomiting	None	1-2x/24hrs	3-5x/ 24hrs	>6x/24hrs, requires IVF
Diarrhea	<2 loose stools/24hrs	2-3 loose stools/24hrs	4-5 loose stools/24hrs	>6 loose stools/24hrs, requires IVF
Irritability	None	Requires more cuddling/ less playful	More difficult to settle	Unable to console
Shivering	None	Present but does not interfere with daily	Interferes with daily activity	Prevents daily activity
Nausea Myalgia Arthralgia Headache Fatigue	None	No interference with daily activity	Interferes with daily activity	Prevents daily activity

Source: Adapted from STN 125408.329, V130_12 Clinical Study Report, Table 9-9

Other solicited AEs, including 'fever' were captured as No (<38C) or Yes (≥38C), and use of analgesics/antipyretics for treatment or prophylaxis was captured as No or Yes.

Unsolicited AEs were events that were spontaneously reported by a subject (or parent/legal guardian) to the site. All unsolicited AEs were collected from Day 1 to Day 22 for participants previously vaccinated and Day 1 to Day 50 for participants who were not previously vaccinated. Unsolicited AEs could be medically attended AEs, defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider. The information pertaining to these events were reported to a qualified site personnel. Unsolicited AEs were graded by the investigator as follows:

- Mild: transient with no limitation in normal daily activity
- Moderate; some limitation in normal daily activity

- Severe: unable to perform daily activity

Follow-Up Study Period
During the follow-up period (through Day 181 or Day 209, respectively for previously vaccinate or not previously vaccine) participant safety data were captured during safety phone calls. Safety data collected during these calls including AEs leading to withdrawal, new onset chronic diseases (NOCDs), serious adverse events (SAEs), ILIs, medically attended AEs (MAAEs) within 30 days after ILI onset, and concomitant medication use related to these events.

Efficacy:
Influenza like illness (ILI) in the study was defined as body temperature of ≥37.8°C (100°F) and at least one of the following: cough, sore throat, nasal congestion, or rhinorrhea. ILI active surveillance was conducted from Day 1 until the end of the influenza season (or until early discontinuation) by weekly telephone calls. Participants with ILI like symptoms, were to have unscheduled visits within 3 to 6 days following symptom onset. All participants received an ILI booklet and guardians/parents were instructed on the onset day ILI to record body temperature until the day they came to the clinic, at which time the ILI booklet would be collected.

At the unscheduled clinic visit, participants had a nasopharyngeal (NP) swab collected for evaluation of the presence of influenza virus (an oropharyngeal swab could have been used if collection an NP swab was not feasible). The swabs were evaluated by RT-PCR and cultured at a central laboratory. Only RT-PCR positive swabs were further characterized by antigenic typing methods to precisely identify the influenza strain(s) collected with the NP-swab. The RT-PCR and culture confirmed influenza cases were evaluated starting >14 days after the last study vaccination (14 days post-single dose in previously vaccinated, or 14 days post-2nd dose in not previously vaccinated).

The evaluation of influenza cases ended at the end of the influenza season. Approximately 30 days after ILI onset, a safety follow-up call was made to determine if subsequent medically attended AEs (MAEEs) occurred, and if so, whether any concomitant medications associated with these events were used.

Immunogenicity:
Immunogenicity assessments by hemagglutination inhibition (HI) assay to measure antibody responses were included for a subset of participants 2 to <9 years of age who were randomly selected to participate during Seasons 2 and 3 and were balanced based on previous influenza vaccination history. Participants had blood draws before each vaccination, and 3 weeks after each vaccination (2 blood draws per participants for participants previously vaccinated and 3 blood draws for participants not previously vaccinated). Testing of samples was performed with Day 1 and Day 22 sera or Day 1, Day 29 and Day 50 sera tested in the same assay run. The HI assay is a widely accepted method of immunogenicity assessment after influenza vaccination. Influenza virus contains on its surface multiple copies of the major glycoprotein, HA, which binds specifically to sialic acid-containing receptors, such as those found on the red blood cell (RBC) plasma membrane. Incubation of the virus with virus specific antibodies prior to the hemagglutination reaction results in an inhibition of the hemagglutination. When dilutions are prepared of anti-sera, the highest dilution which still prevents hemagglutination of the virus with RBCs, provides a means to quantify virus specific antibodies in subject serum samples.

Additional immunogenicity testing, (b) (4) was performed on serum samples collected before vaccination on Day 1 and on Day 22 for previously vaccinated

participants and Day 1, Day 29, and Day 50, for all not previously vaccinated participants. When dilutions of anti-sera are prepared and incubated with a constant input of homologous influenza strains, the highest dilution that neutralizes at least 50% of the viral infection of the cells in tissue culture, provides a means to quantify virus specific antibodies in subject serum samples.

The reference strains used in the assessment of antigenicity were for:

- Southern Hemisphere (SH) 2017 (Season 1) - A/Singapore/GP1908/2015 IVR-180 (H1N1), A/HongKong/4801/2014 (H3N2), B/HongKong/259/2010 (B Victoria), and B/Utah/9/2014 (B Yamagata).

- Northern Hemisphere (NH) 2017/2018 (Season 2): identical for SH 2017 except that the H3N2 strain was A/Singapore/GP2050/2015 (H3N2).

- NH 2018/19 (season 3): all strains were replaced except for H1N1; A/North Carolina 04/2016 (H3N2), B/Iowa/06/2017 (B Victoria), B/Singapore/INFTT-16-06 10/2016 (B Yamagata).

Testing was conducted by Seqirus-designated qualified laboratory personnel ((b) (4)) who were blinded to the treatment assignment and the visit.

6.1.8 Endpoints and Criteria for Study Success

Please see Section 6.1.1 of the clinical review memo.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The analysis of study data was based on the final Statistical Analysis Plan, version 5.0 (dated 27 September 2019).

Sample Size Calculations:

Primary Efficacy Objective: 2 to <18 years of age

With an assumed vaccine effectiveness of 45% and an influenza attack rate (in comparator group) of 8%, the estimated sample size was determined to be 4814 evaluable participants (2407 evaluable subject/treatment group) to attain 298 influenza like illness case events. Accounting for early dropout and uncertainty about the assumed parameters, 5349 participants were planned to be enrolled to demonstrate the lower limit of the 2-sided 95% CI for the VE >20% for the primary endpoint assessment with ~90% power.

Co-Primary Efficacy Objective: 3 to <18 years of age

With an assumed vaccine effectiveness of 50%, 381 observed confirmed influenza like illness case events would be needed to demonstrate that the lower limit of the 2-sided 95% CI for the VE>30% with ~90% power. The estimated sample size was determined to be 6350 evaluable participants (3175 evaluable participants/treatment group), assuming the attack rate was 8% and VE was 5%

Subgroup Analyses:

The efficacy, immunogenicity, and safety analyses were performed stratified based on different subgroups, including age, prior vaccination history, race, sex, pre-vaccination HI titer, country/region, or season/year treated. The age stratifications were based on the following subgroups for the listed analyses:

- 2 to <4 years: efficacy

- 2 to <6 years: safety
- 2 to <9 years: efficacy, immunogenicity, safety
- 2 to <18 years: efficacy, safety
- 3 to <18 years: efficacy, safety
- 4 to <18 years: efficacy, safety
- 9 to <18 years: efficacy, safety

Reviewer Comment:

The study enrollment was stratified by the following two age subgroups: 2years through 8 years and 9 years through 17 years, such the ~50% of study population was in each age cohort.

Statistical Methods:

Efficacy Data-

If <20% of participants are without efficacy data, then the analyses will be run on FAS and PPA and no further statistical evaluations will be performed. If observations are missing for ≥20% or more of participants, the missing mechanism will be analyzed by vaccine group using a newly created variable indicated whether a participants' efficacy-value is missing or not (1= efficacy record present, 0= efficacy record not present). It will be tested by chi-square test, if the proportion of missing observations/participants varies significantly between vaccine groups. If the differences is significant with $p < 0.05$, then a sensitivity analysis will be performed of the primary efficacy analysis imputing randomly X% (from 0% to 100% in 10% increments) of missing data as PCR-confirmed cases.

Immunogenicity Data-

Missing immunogenicity values are considered 'missing completely at random' (MCAR) and imputations methods will not be used.

Safety Data-

The analyses were done without adjustment for missing values, no imputations of missing solicited or unsolicited AES were used.

Protocol Amendments:

Protocol version 5- Amendment 4 issued 13 December 2018, major revisions in this and prior amendments include the following:

- Limited subgroup analyses by age:
  - To support US FDA PMR commitment: vaccine efficacy in 4 to 17 years
    - 4 to 8 years and 4 to 17 years
  - To support approval in children 2 years and older in European Union (VE 2 to 8 years and 9 years to 17 years)
  - For immunogenicity and safety: 4 years to 8 years was added
- Interim analysis after the 2nd influenza season was removed and updated to be conditional based on sufficient # of accrued cases based on needs of sponsor. Test for futility from the interim analysis was removed because specific VE questions would be unanswered
- Because the overall influenza event rate observed in the 1st study season was higher compared to original assumptions, the assumed event rate in the non-influenza comparator group was updated to 8% (from 4%). Adjustment to the sample size and required number of influenza events were revised to maintain study power.

- Adjusted the aVE assumption to 50% based on information from randomized clinical trials in children. Co-primary aVE assumption was changed to aVE with lower limit of 2-sided 95% CI unchanged at >20%.
- The primary/co-primary endpoint were reversed in order of testing such that 2 to 17 years was evaluated first at the primary endpoint, then 3 to 17 years as the co-primary endpoint.

Significant Changes in the Conduct of the Study & Planned Analyses:

- Erroneously the relevant diary card for parents of ≥6 years of age participants to report solicited AEs included two extra items (runny nose and sore throat) that were not pre-defined solicited AEs, as per protocol. The data collected for these two extra items were included in the study data tabulation model (SDTM) dataset and the full study tables, listing and figures (appendices), but they were not included in the clinical study report in text tables.

6.1.10 Study Population and Disposition

Study V130_12 was conducted at 39 sites in eight countries (7 sites-Philippines, 5 sites-Estonia, 2 sites-Thailand, 10 sites-Finland, 6 sites-Poland, 6 sites-Lithuania, 2 sites-Australia, and 1 site-Spain). The study was initiated on 25 May 2017 and was completed on 30 September 2019 and the study was conducted over 3 influenza seasons: Southern Hemisphere 2017 (Season 1), Northern Hemisphere 2017-2018 (Season 2), and Northern Hemisphere 2018-2019 (Season 3).

6.1.10.1 Populations Enrolled/Analyzed

A total of 4514 participants 2 to <18 years of age were enrolled and randomized: 2258 in QIVc arm and 2256 in comparator-Menveo arm. Of these participants, 4513 participants were vaccinated, and 4496 completed the study.

Relevant analysis populations:

- All Enrolled: all screened participant who provided informed consent, received a subject identification, and provided baseline assessments
- All Exposed Set: all participants in the All Enrolled Set who received a study vaccination
- Safety Set (Solicited): Participants in the Exposed Set who had gone through any assessment of local and systemic site reaction and/or assessment of any use of analgesics/antipyretics
- Safety Set (Unsolicited): Participants in the Exposed Set who had gone through any AE assessment, i.e., a subject did not have any AE to be included in this population
- Overall Safety Set: Participants in the Solicited and Unsolicited Safety Sets
- Full Analyses Set (FAS): Participants who received at least 1 dose of the study vaccine and were evaluated for efficacy from 14 days after the last vaccination
- Full Analyses Set Immunogenicity: Participants who received at least one dose of study vaccine and provided evaluable serum samples at both baseline and after the last vaccination. The last vaccination was Visit 2 for previously vaccinated participants, and Visit 3 for no previously vaccinated participants. In case of vaccination error, participants were analyses as randomized
- Per Protocol Efficacy/Immunogenicity Set: Correctly received the vaccine (received the vaccine to which the participants were randomized and at the scheduled time points), had no protocol deviations, and were not excluded due to other reasons. In case of vaccination error participants in the PPS were analyses as randomized and participants who received the wrong vaccination were excluded from the PPS.

Subgroup Analyses:
The efficacy analyses were performed stratified for the following subgroups for those subgroups with confirmed ILI cases ≥10:

- Age: 2 through 3 years, 2 through 8 years, 2 through 17 years, 3 through 18 years, 4 through 18 years, and 9 through 17 years
- Influenza vaccination history
- Race, sex, country/region, and season/year

Protocol Deviations:
Major protocol violations were reported in 126 participants (2 through 17 years of age): 54 (2.4%) in the QIVc group and 72 (3.2%) in the Menveo group. The most common deviation observed across groups was 'investigational product administrations/study treatment', with 64 reported events, most of which (54) were due to the administration of vaccine dose #2 given outside the Day 29 (± 3 days) window after Dose 1. The next most frequently reported deviation was 'procedures/tests", with 53 events reported, most of which were missed blood draws, reported in 20 participants (0.9%) in the vaccine group and 33 events (1.5%) in the comparator group. Other reported major protocol deviations were reported in less than 1% of participants in each group and included 'disallowed medications subject' and 'informed consent.' There were 4 participants excluded from the FAS efficacy population, 1 in the QIVc group and 3 in the Menveo group, all due to 'early terminated prior to influenza surveillance period.'
There were 33 participants 2 through 8 years of age who were excluded from the PPS immunogenicity populations, included 15 (4.0%) in the QIVc group and 18 (4.8%) in the Menveo group. The most common reason was due to dose 2 not administered on Day 29 (± 3) days after dose 1, reported in 12 (3.2%) QIVc participants and 6 (1.6%) Menveo participants.

Reviewer Comment: *The rates of major protocol deviations were relatively low across groups and unlikely to have affected the study efficacy or immunogenicity findings substantially.*

6.1.10.1.1 Baseline Characteristics and Demographics

Overall Study V130_12 Study Enrollment (N= 4514):

- Geographic location:
  - Southern hemisphere: 2395 (53.1%)
  - Northern hemisphere: 2119 (46.9%)
- Influenza season:
  - Season 1: 2395 (53.1%)
    - Philippines (39.9%), Thailand (8.8%), Australia (8.9%)
  - Season 2: 919 (20.4%)
    - Estonia (13.3%), Finland (7.1%)
  - Season 3: 1200 (26.6%)
    - Estonia (13.2%), Poland (6.6%), Lithuania (6.5%), Finland (0.2%), Spain (0.1%)
- Influenza vaccination history
  - 2 through 17 years
    - previously vaccinated: 65.9%
    - not previously vaccinated: 34.1%
  - 2 through 8 years
    - previously vaccinated: 32.8%
    - not previously vaccinated: 67.2%

The following table provides an overview of the demographic and baseline characteristics of enrolled participants across study groups.

Table 4: Study V130_12 Baseline and Demographic Characteristics Across Study Groups

Demographic Characteristic	**QIVx (N=2258) X (%)**	**Menveo (N=2256) X (%)**
Country:	--	--
Australia	96 (4.3%)	99 (4.4%)
Estonia	599 (26.5%)	599 (26.6%)
Finland	168 (7.4%)	158 (7.0%)
Lithuania	142 (6.3%)	150 (6.6%)
Philippines	902 (39.9%)	898 (39.8%)
Poland	147 (6.5%)	151 (6.7%)
Spain	3 (0.1%)	2 (0.1%)
Thailand	201 (8.9%)	199 (8.8%)
Previously vaccinated	1488 (65.9%)	1487 (65.9%)
Not previously vaccinated	770 (34.1%)	769 (34.1%)
Season 1	1199 (53.1%)	1196 (53.0%)
Season 2	459 (20.3%)	460 (20.4%)
Season 3	600 (26.6%)	600 (26.6%)
Sex Ratio M:F (%)	1152:1106 (51%:49%)	1174:1082 (52%:48%)
Age Mean (SD)	8.7 (4.0)	8.9 (4.1)
Age Median (min, max)	8.0 (2, 17)	8.0 (2, 17)
Age Group:	--	--
2 through 17 years	2258 (100%)	2256 (100%)
2 through 8 years	1146 (50.8%)	1143 (50.7%)
9 through 17 years	1112 (49.2%)	1113 (49.3%)
2 through 3 years	212 (9.4%)	220 (9.8%)
4 through 17 years	2046 (90.6%)	2036 (90.2%)
Racial origin:	--	--
White	1140 (50.5%)	1139 (50.5%)
Black/A.A.	1 (<0.1%)	0
Asian	1106 (49.0)	1100 (48.8%)
N.Hawaiian/P.I	0	2 (0.1%)
Am.Indian/A.N	0	0
Other	11 (0.5%)	15 (0.7%)
Ethnicity:	--	--
Hispanic/Latino	11 (0.5%)	11 (0.5%)
Not H/L	2245 (99.4%)	2245 (99.5)

Source: Adapted from STN 125408.329, CSR Study V130_12, Table 10-6

Reviewer Comment*:*

- As shown above the baseline and demographic characteristics were comparable across study groups and were generally representative of the countries included in the study. The majority of participants were either White or Asian, corresponding accordingly with the countries that had the greater study enrollment. Notably, the study was not representative

of racial/ethnic composition of US populations, specifically only 1 Black participant and only 22 participants with Hispanic ethnicity.

- The study report for Study V130_12 includes data in children 2 years through 17 years of age, however study was originally designed to evaluate the safety and efficacy of QIVc in children 4 years through 17 years of age. Under the IND, the protocol was revised to permit inclusion of children 2 through 3 years (<4 years) to align with other regulatory agencies.. There were 432 randomized participants 2 years through 3 years of age (9.6% of total participants), including 212 QIVc recipients and 220 placebo recipients. In a subset of study participants 2 through <9 years of age, a descriptive analyses of immunogenicity endpoints were conducted.
    - The agreed Pediatric Study Plan requires that another study, V130_10 evaluate the safety and immunogenicity (inferred effectiveness) of QIVc in children 6 months through 3 years (<4 years). However, in this reviewer's opinion Study V130_12 is an appropriately designed study to assess the safety and efficacy of QIVc in children 2 years through 3 years and the number of QIVc recipients is sufficient to draw meaningful conclusions as required under the Pediatric Research Equity Act (PREA). The evaluation of QIVc in V130_02 in children 2 through <4 years constitute an appropriate assessment because the study evaluated the safety and efficacy of QIVc compared to an active comparator with a sufficient number of participants enrolled (432) between the age of 2 through <4 years.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
N/A

6.1.10.1.3 Subject Disposition

The following table provide an overview of study participant disposition across groups.

Table 5 Study V130_12 Participant Disposition

	Flucelvax N=2258	**Menveo N=2256**	**Total N=4514**
Enrolled	2258	2256	4514
Vaccinated	2258 (100%)	2255 (99.96%)	4513 (99.98%)
Completed study	2249 (99.6%)	2247 (99.6%)	4496 (99.6%)
Premature discontinuations	9 (0.4%)	9 (0.4%)	18 (0.4%)
Death	0	1 (0.4%)	1 (0.02%)
Adverse event	0	0	0
Consent withdrawn	3 (0.13%)	3 (0.13%)	6 (0.13%)
Lost to follow-up	5 (0.22%)	2 (0.9%)	7 (0.16%)
Administrative reason	0	0	0
Protocol violations	0	0	0
Other	1 (0.04%)	3 (0.13%)	4 (0.09%)

Source: Adapted from STN 125408.329, CSR Study 130_12, Table 10-1

Across study groups, 99.6% of participants completed the study. The majority of premature study discontinuations were due to lost to follow-up. There was 1 study discontinuation due to death in the comparator-Menveo arm, and there were no study discontinuations due to an adverse event.

Reviewer Comment: The proportion of participants with premature study discontinuations was low (0.4%) and similar across study groups. The most common reason was lost to follow-up, which was over a 6-month time period and occurring in 9 participants in each study group.

6.1.11 Efficacy Analyses

The following table provides the overall vaccine efficacy of QIVc compared to Menveo comparator against all influenza viral subtypes and against individual influenza viral subtypes antigenically similar to the subtypes in the vaccine. This table will be included in Section 14.2 of the revised USPI for Flucelvax Quadrivalent with the approval of this application.

Table 6: V130_12 Overall Vaccine Efficacy of QIVc against 1st Occurrence RT-PCR Confirmed or Culture Confirmed Influenza in Participants 2 through 17 years of age– FAS Efficacy

	Participants	**Cases of Influenza**	**Attack Rate (%)**	**Vaccine Efficacy %* [95% CI]**
RT-PCR/CCI**	--	--	--	--
QIVc	2257	175	7.8	54.6% [**45.7**, 62.1]
Comparator	2252	364	16.2	--
CCI**	--	--	--	--
QIVc	2257	115	5.1	60.8% [51.3, 68.5]
Comparator	2252	279	12.4	--
Antigenically Matched CCI**	--	--	--	--
QIVc	2257	90	4.0	63.6% [53.6, 71.5]
Comparator	2252	236	10.5	- -

Source: Adapted from STN 125408.329. Full-Analysis Set (FAS) Efficacy – *Efficacy, which included all participants randomized, received a study vaccination and provided efficacy data.**CCI: Culture confirmed influenza. [2]Efficacy against influenza was evaluated over three influenza seasons, SH 2017, NH 2017-18 and NH 2018-19. QIVc met the pre-defined success criterion defined as the lower limit of the two-sided 95% CI of absolute vaccine efficacy greater than 20%.

Reviewer Comment:

Vaccine efficacy of QIVc against influenza disease based on clinically efficacy primary study endpoints in pediatric age participants 2 years through 17 years of age, was met with the lower limit of the 95% CI of the 2-sided 95% CI of absolute vaccine efficacy >20%. VE was demonstrated for the 1st RT-PCR confirmed, or culture confirmed influenza, with comparable results observed when evaluating only culture confirmed influenza and antigenically matched/culture confirmed influenza.

6.1.11.1 Analyses of Primary Endpoints

Primary Efficacy Objectives: VE in participants 2 to <18 years & VE in participants 3 to <18 years

The two primary objectives were to demonstrate protection of the study vaccine, QIVc compared to the active comparator vaccine (MenACWY vaccine) against illness caused by RT-PCR- or culture-confirmed influenza, community acquired influenza Type A or B strains that occurred more than 14 days after the last vaccination until the end of the influenza season.

The 1st primary objective was assessed in participants 2 years through 17 years (<18 years) using the FAS Efficacy-1 analysis set and was demonstrated if the LL of the 2-sided CI of the absolute VE estimate was above 20%.

The 2nd primary objective was assessed in participants 3 years through 17 years (<18 years) using the FAS Efficacy-2 analysis set and was demonstrated if the LL of the 2-sided aVE was above 30%. The results of both primary endpoints are shown in the table below.

Table 7: Study V130_12 Primary Objectives- Number of Participants with 1st-Occurrence RT-PCR-Confirmed or Culture Confirmed Influenza and Absolute Vaccine Efficacy [95% CI], Overall in Participants 2 years to <18 Years of Age and 3 years through 17 Years of Age – FAS Efficacy

	QIVc #Cases (attack rate)	**Comparator** #Cases (attack rate)	**aVE [95% CI]**	**Success Criteria Met***
2 to <18years	*N=2257*	*N=2252*	--	--
FAS-Eff1	175 (7.8%)	364 (16.2%)	54.63%	--
	--	--	[**45.67**, 62.12]	Yes
3 to <18years	*N=2208*	*N=2201*	--	--
FAS-Eff2	171 (7.7%)	351 (15.9%)	54.03%	--
	--	--	[**44.8**, 61.71]	Yes

Source: BLA 125408.329, Study V130_12 CSR, Table 11-2. N: total number participants. FAS-Efficacy: Full analyses set included all participants who received at least one dose of study vaccine and were evaluated for efficacy from 14 days after last vaccination. *FAS-Eff1 for participants 2 to <18 years study success criteria required the lower limit of the 2-sided CI of the absolute VE estimate to be above 20%. FAS-Eff2 for all participants 3 to <18 years study success criteria required the lower limit of the 2-sided CI of the absolute VE estimate to be over 30%.

There were a total of 2444 ILI cases (1193 QIVc group, 1251 comparator group) reported in 1685 participants (791 QIVc participants, 894 comparator participants). As shown in the table above, the lower bound of the 2-sided 95% CI for vaccine efficacy was 45.67% for QIVc compared to MenACWY for subject 2 through 17 years (<18 years) and was 44.8% for QIVc compared to MenACWY for participants 3 through 17 years (<18 years).

Reviewer Comment:
The results of both primary analyses met the protocol pre-specified criteria for demonstration of efficacy.

6.1.11.2 Analyses of Secondary Endpoints

Secondary Efficacy Objective #1: VE by RT-PCR or Culture Confirmed by Strain
The following table provides the VE estimates of QIVc compared to the non-influenza comparator determined by the 1st occurrence of either RT-PCR and/or culture confirmed influenza due to any Type A and B strain in participants 2 years through 17 years.

Table 8: Study V130_12 Secondary Objective-Number of Participants with 1st Occurrence RT-PCR Confirmed or Culture Confirmed Influenza and Absolute VE [95% CI] Overall and by Strain in Participants 2 years through 17 years -FAS1 Efficacy

STRAIN	QIVc #Cases (attack rate) *N=2257*	Comparator #Cases (attack rate) *N=2252*	aVE [95% CI]
Any Strain	175 (7.8%) --	364 (16.2%) --	54.63% [**45.67**, 62.12]
Type A	96 (4.3%)	214 (9.5%)	56.97% [45.25, 66.18]
A/H1N1	*21 (0.9%)*	*105 (4.7%)*	80.63 [69.21, 87.94]
A/H3N2	*60 (2.7%)*	*102 (4.5%)*	42.08 [20.32, 57.89]
Type B	*81 (3.6%)*	*150 (6.7%)*	47.62% [31.36, 60.0]

Source: BLA 125408.329, Study V130_12 CSR, Table 11-3. N: total number participants. FAS-Efficacy: Full analyses set included all participants who received at least one dose of study vaccine and were evaluated for efficacy from 14 days after last vaccination. FAS-Eff1 for participants 2 to <18 years.

Secondary Efficacy Objective #2: VE by RT-PCR or Culture Confirmed by Strain
The following table provides the VE estimates of QIVc compared to the non-influenza comparator determined by the 1st occurrence of either RT-PCR and/or culture confirmed influenza due to any Type A and B strain in participants 3 years to <18 years.

Table 9: Study V130_12 Secondary Objective-Number of Participants with 1st Occurrence RT-PCR Confirmed or Culture Confirmed Influenza and Absolute VE [95% CI] Overall and by Strain in Participants 3 years through 17 years -FAS2 Efficacy

STRAIN	QIVc #Cases (attack rate) *N=2208*	Comparator #Cases (attack rate) *N=2201*	aVE [95% CI]
Any Strain	171 (7.7%) --	351 (15.9%) --	54.03% [**44.8**, 61.71]
Type A	94 (4.3%)	204 (9.3%)	55.98% [43.78, 65.52]
A/H1N1	*20 (0.9%)*	*97 (4.4%)*	80.38 [68.23, 87.88]
A/H3N2	*59 (2.7%)*	*99 (4.5%)*	41.24 [18.89, 57.44]
Type B	*79 (3.6%)*	*147 (6.7%)*	47.72% [31.27, 60.23]

Source: BLA 125408.329, Study V130_12 CSR, Table 11-3. N: total number participants. FAS-Efficacy: Full analyses set included all participants who received at least one dose of study vaccine and were evaluated for efficacy from 14 days after last vaccination. FAS-Eff2 for participants 3 to <18 years.

Reviewer Comment:
The results of both secondary efficacy analyses by VE by strain demonstrate greater VE against A/H1N1, followed by B strain, and then least VE against A/H3N2. However the overall study results support the efficacy of QIVc.

6.1.11.3 Subpopulation Efficacy Analyses

Vaccine Efficacy: 2 years through 3 years (<4 years)

The following table provides the VE estimates of QIVc compared to the non-influenza comparator determined by the 1st occurrence of either RT-PCR and/or culture confirmed influenza due to any Type A and B strain in participants 2 years through 3 years (<4 years).

Table 10: Study V130_12 Number of Participants with 1st Occurrence RT-PCR Confirmed or Culture Confirmed Influenza and Absolute VE [95% CI] by Strain Overall and by Strain in Participants 2 through 3 years - FAS Efficacy

STRAIN	**QIVc** #Cases (attack rate) *N= 212*	**Comparator** #Cases (attack rate) *N= 220*	**aVE [95% CI]**
Any Strain	21 (9.9%) --	54 (24.5%) --	62.66% [38.06, 77.49]
Type A	13 (6.1%) --	35 (15.9%) --	63.69% [31.21, 80.83]
A/H1N1	*3 (1.4%)* --	*19 (8.6%)* --	85.79% [51.76, 95.81]
A/H3N2	*8 (3.8%)* --	*16 (7.3%)* --	48.71% [-20.73, 78.21]
Type B	*8 (3.8%)* --	*19 (8.6%)* --	57.79% [3.16, 81.6]

Source: Adapted from STN 125408.329, Study V130_12 CSR, Table 11-4. N: total number participants. FAS-Efficacy: Full analyses set included all participants who received at least one dose of study vaccine and were evaluated for efficacy from 14 days after last vaccination.

Antigenically Matched Culture-Confirmed Influenza (2 through 3 years):
The culture confirmed VE estimates of QIVc compared to the non-influenza comparator determined by the 1st occurrence of culture confirmed influenza by antigenically matched strains for participants 2 through 3 years are presented below with the cases #s (attack rates%).

- *All Matched Strains:* 77.08% [52.27, 89.0]
  - 9 (4.2%) QIVc vs 36 (16.4%) comparator
- A/H1N1: 84.07% [45.39, 95.35]
  - 3 (1.4%) QIVc vs 17 (7.7%) comparator
- A/H3N2: 80.73% [9.75, 95.89]
  - 2 (0.9%) QIVc vs 9 (4.1%) comparator
- B/Yamagata: 63.73% [-14.24, 88.48]
  - 4 (1.9%) QIVc vs 11 (5.0%) comparator
- B/Victoria: Not assessed
  - 0 case QIVc vs 0 cases comparator

Reviewer Comment:
As mentioned in a previous reviewer comment, the current clinical efficacy supplement includes data on children 2 years through 3 years of age, an age sub-cohort not included in the original protocol, but subsequently amended under the IND. The study includes 432 randomized participants in this age sub-cohort (9.6% of total participants), including 212 QIVc recipients and 220 placebo recipients. The efficacy data presented support a pediatric assessment in children 2 years through 3 years, as required under the Pediatric Research Equity Act (PREA).

Vaccine Efficacy by Age: 2 through 8 years

The following table provides the VE estimates of QIVc compared to the non-influenza comparator determined by the 1st occurrence of either RT-PCR and/or culture confirmed influenza due to any Type A and B strain in participants 2 years through 8 years.

Table 11: Study V130_12 Secondary Objective- Number of Participants with 1st Occurrence RT-PCR Confirmed or Culture Confirmed Influenza and Absolute VE [95% CI] by Strain Overall and by Stain in Participants 2 through 8 years - FAS Efficacy

STRAIN	**QIVc** #Cases (attack rate) *N=1146*	**Comparator** #Cases (attack rate) *N=1142*	**aVE [95% CI]**
Any Strain	123 (10.7%) --	234 (20.5%) --	50.51% [38.4, 60.2]
Type A	68 (5.9%) --	141 (12.3%) --	54.12% [38.7, 65.6]
A/H1N1	*17 (1.5%)* --	*81 (7.1%)* --	79.9% [66.2, 88.1]
A/H3N2	*39(3.4%)* --	*57 (5.0%)* --	32.8% [-0.96, 55.3]
Type B	*57 (5.0%)* --	*93 (8.1%)* --	40.9% [16.96, 57.1]

Source: BLA 125408.329, Study V130_12 CSR, Table 11-5. N: total number participants. FAS-Efficacy: Full analyses set included all participants who received at least one dose of study vaccine and were evaluated for efficacy from 14 days after last vaccination.

Antigenically Matched Culture-Confirmed Influenza (2 through 8 years):
The culture confirmed VE estimates of QIVc compared to the non-influenza comparator determined by the 1st occurrence of culture confirmed influenza by antigenically matched strains for participants 2 through 8 years are presented below with the cases #s (attack rates%).

- *All Matched Strains*: 63.04% [50.66, 72.32]
  - 64 (5.6%) QIVc vs 164 (14.4%) comparator
- A/H1N1: 82.63% [68.63, 90.38]
  - 13 (1.1%) QIVc, 72 (6.3%) comparator
- A/H3N2: 45.81% [-4.26, 71.84]
  - 14 (1.2%) QIVc, 25 (2,2%) comparator
- B/Yamagata: 48.08% [22.23, 65.34]
  - 36 (3.1%) QIVc, 68 (6.0%) comparator
- B/Victoria: NA
  - 1 case QIVc vs 0 cases comparator

Vaccine Efficacy by Age: 9 through 17 years
The following table provides the VE estimates of QIVc compared to the non-influenza comparator determined by the 1st occurrence of either RT-PCR and/or culture confirmed influenza due to any Type A and B strain in participants 9 years through 17 years.

Table 12: Study V130_12 Number of Participants with 1st Occurrence RT-PCR Confirmed or Culture Confirmed Influenza and Absolute VE [95% CI] by Strain Overall and by Strain in Participants 9 through 17 years - FAS Efficacy

STRAIN	**QIVc** #Cases (attack rate) *N= 1111*	**Comparator** #Cases (attack rate) *N= 1110*	**aVE [95% CI]**

Any Strain	52 (4.7%) --	130 (11.7%) --	61.85% [47.37, 72.34]
Type A	28 (2.5%) --	73 (6.6%) --	62.58% [42.15, 75.8]
A/H1N1	*4 (0.4%)* --	*24 (2.2%)* --	83.46% [52.31, 94.26]
A/H3N2	*21 (1.9%)* --	*45 (4.1%)* --	53.93% [22.66, 72.5]
Type B	*24 (2.2%)* --	*57 (5.1%)* --	59.37% [34.54, 74.79]

Source: Adapted from STN 125408.329, Study V130_12 CSR, Table 11-5. N: total number participants. FAS-Efficacy: Full analyses set included all participants who received at least one dose of study vaccine and were evaluated for efficacy from 14 days after last vaccination.

Antigenically Matched Culture-Confirmed Influenza (9 through 17 years):
The culture confirmed VE estimates of QIVc compared to the non-influenza comparator determined by the 1st occurrence of culture confirmed influenza by antigenically matched strains for participants 9 through 17 years are presented below with the cases #s (attack rates%).

- *All Matched Strains:* 64.78% [44.84, 77.51]
  - 26 (2.3%) QIVc vs 72 (6.5%) comparator
- A/H1N1: 80.05% [41.64, 93.18]
  - 4 (0.4%) QIVc vs 20 (1.8%) comparator
- A/H3N2: 44.76% [-49.43, 79.58]
  - 6 (0.5%) QIVc vs 11 (1.0%) comparator
- B/Yamagata: 57.89% [24.29, 76.58]
  - 16 (1.4%) QIVc vs 37 (3.3%) comparator
- B/Victoria: NA
  - 1 case QIVc vs 4 cases comparator

Reviewer Comment:
The results of vaccine efficacy analyses by age demonstrate numerically higher VE in older participants than younger participants, though both age cohorts had overall VE by strain and VE by antigenically match culture confirmed influenza that paralleled the overall primary analyses for VE in all participants 2 through 17 years.

Vaccine Efficacy: By Season

For all study participants (2 years through 17 years): The absolute VE estimates against RT-PCR or culture confirmed Type A or Type B influenza are summarized below for Season 1 (Southern Hemisphere 2017), Season 2 (Northern Hemisphere 2017-18), and Season 3 (Northern Hemisphere 2018-19).

Table 13: Study V130_12 Number of Participants with 1st-Occurrence RT-PCR Confirmed or Cultured Confirmed Influenza and Absolute VE [95% CI] by Season- FAS Efficacy

Season	**QIVc** #Cases (attack rate) *N= 2257*	**Comparator** #Cases (attack rate) *N= 2252*	**aVE [95% CI]**
Season 1- SH 2017 RT-PCR/Culture Conf.	-- 89 (7.4%)	-- 193 (16.2%)	-- 56.58% [44.18, 66.22]
Season 1- SH 2017 Culture Conf/ Matched	-- 35 (2.9%)	-- 98 (8.2%)	-- 65.73 [49.58, 76.7]
Season 2- NH 2017-18	--	--	--

RT-PCR/Culture Conf.	47 (10.2%)	80 (17.4%)	44.16% [19.93, 61.05]
Season 2- NH 2017-18 Culture Conf/Matched	-- 28 (6.1%)	-- 59 (12.9%)	-- 54.54% [28.7, 71.01]
Season 3- NH 2018-19 RT-PCR/Culture Conf	-- 39 (6.5%)	-- 91 (15.2%)	-- 59.49% [41.03, 72.18]
Season 3-NH2018-19 Culture Conf/Matched	-- 27 (4.5%)	-- 79 (13.2%)	-- 67.59% [49.81, 79.07]

Source: Adapted from STN 25408.329, Study V130_12 CSR, Table 11-6. N: total number participants. FAS-Efficacy.

Reviewer Comment:

VE by season for appeared to be greatest in Season 1 (SH 2017) and Season 3 (NH 2018-19).

Vaccine Efficacy: By Sex, Race

For all study participants (2 year through 17 years): Vaccine Efficacy 1st occurrence of RT-PCR confirmed influenza

- Sex:
  - Male- 54.7% [42.04, 64.59]
  - Female- 54.47% [40.64, 65.08]
- Race:
  - White participants: 54.74% [41.54, 64.96]
  - Asian participants: 53.7% [40.24, 64.13]

Reviewer Comment:

There was no difference observed in VE estimates based on sex or between White and Asian participants. There were too few participants in other racial groups to estimate vaccine efficacy, though it is not anticipated that VE would differ based on racial/ethnic origin. Though not presented, there were no differences observed in VE based on prior influenza vaccination history as well.

6.1.11.4 Immunogenicity Analyses

Reviewer Comment:

The immunogenicity analyses in Study V130_12 were descriptively evaluated in a subset of study participants in Seasons 2 and 3. As noted below, the total # of QIVc recipients included in the FAS immunogenicity set for Season 2 was 210 participants and 145 participants in Season 3. With the AA of QIVc in children 4 years through <18 years of age in 2016, non-inferiority of QIVc compared to TIVc was demonstrated based on the respective success criteria for each primary immunogenicity endpoints (ratio of GMTs and seroconversion rates) to each strain separately in ~ 1000 QIVc participants. The immunogenicity analyses for Study V130_12 are therefore presented in this section to support the clinical efficacy study findings only, rather than to inform labeling for QIVc.

Secondary Immunogenicity Analyses in Subset of Participants: 21 days post-vaccination

Hemagglutination Inhibition (FAS Immunogenicity Set):

The immunogenicity of QIVc was characterized at 3 weeks after the last vaccine by hemagglutination inhibition (HI assay) to the 4 viral strains included in the vaccines in a subset of 751 participants 2 years through 8 years of age (<9 years) who were enrolled in Season 2 (n=432) and Season 3 (n=319), of which 721 were included in the FAS Immunogenicity. The vaccine strain composition changed between seasons-specifically Type A/H3N2, Type B/Yamagata, and Type B/Victoria were updated. The immunogenicity results are presented by season, even in the case where the strain did not change (A/H1N1). For each assay the following measures were

derived: GMTs (shown below in table), GMR, SC rates, and the % of participants with HI titers ≥1:40. These findings were *descriptive without formal hypothesis testing.*

Table 14: Geometric Mean Titer [95% CI] and Geometric Mean Ratio [95% CI], 3 Weeks After Last Vaccination[b], Season 2 and Season 3, HI Assay-FAS Immunogenicity HI

	QIVc Season 2 N=210	**Comparator Season 2** N=212	**QIVc Season 3** N=154	**Comparator Season 3** N=145
A/H1N1 Day 22/50	283.45 [249.22, 322.38]	49.20 [43.24, 55.98]	380.70 [283.12, 511.91]	48.22 [36.14, 64.32]
GMR HI Titer	5.76 [5.06, 6.55]	1.00 [0.88, 1.14]	9.73 [7.24, 13.09]	1.23 [0.92, 1.64]
A/H3N2 Day 22/50	168.73 [150.87,188.7]	96.27 [86.05, 107.7]	67.64 [57.03, 80.24]	16.73 [14.17, 19.77]
GMR HI Titer	1.74 [1.56, 1.95]	0.99 [0.89, 1.11]	4.14 [3.49, 4.91]	1.02 [0.87, 1.21]
B/Victoria Day 22/50	45.25 [39.73, 51.54]	11.94 [10.48, 13.60]	66.82 [51.29, 87.04]	11.94 [9.23, 15.44]
GMR HI Titer	3.79 [3.33, 4.32]	1.00 [0.88, 1.14]	7.01 [5.38, 9.14]	1.25 [0.97, 1.62]
B/Yamagata Day 22/50	52.81 [45.77, 60.94]	12.34 [10.68, 14.24]	108.49 [85.16, 138.22]	21.68 [17.11, 27.46]
GMR HI Titer	4.63 [4.01, 5.34]	1.08 [094, 1.25]	5.27 [4.14, 6.72]	1.05 [0.83, 1.33]

Source: Adapted from sBLA 125408.329, CSR for V130_12, Table 11-10,
HI-hemagglutination-inhibition. Comparator: Menveo for 1st dose-Day 1 and saline placebo for 2nd dose-Day 29, if required.
Adjusted GMTs are listed above and were calculated assuming log-normal distribution of the titers and were completed by providing minimum, maximum and median titers for each vaccine group.
QIVc composition for Season 2 (NH 17/18 season) by strain consisted of A/Singapore/GP1908/2015 IVR-180 (H1N1), A/Singapore/GP2050/2015 (H3N2), B/Utah/9/2014 (B Yamagata), and B/Hong Kong/259/2010 (B Victoria). The Season 3 (NH 18/19) QIVc composition strains consisted of A/Singapore/GP1908/2015 IVR-180
(H1N1), A/North Carolina 04/2016 (H3N2), B/Singapore/INFTT-16-06 10/2016 (B Yamagata), and B/Iowa/06/2017 (B Victoria).

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

The observed GMRs for each of the two seasons evaluated were higher for QIVc group than the comparator group, for the A/HIN1 was 5.76 and 9.73; for A/H3N2 was 1.74* and 4.14; for B/Victoria was 3.79 and 7.01, and for B/Yamagata was 4.63 and 5.27. For the comparator group the GMRs ranged from 0.99 to 1.25. Though not shown, the findings from the PPS Immunogenicity set were similar to those shown above for FAS Immunogenicity.

HI Seroconversion Rates (FAS Immunogenicity Set):
Seroconversion was defined as the following for participants with the following

- Pre-vaccination HI titer <1:10, then post- vaccination HI titer ≥1:40, or
- Pre-vaccination HI titer ≥1:10, then post-vaccination HI titer ≥4-fold increase

The post-vaccination titer was on Day 22 for those previously vaccinated receiving a single dose, or Days 29 or 50 for those not previously vaccinated participants receiving 2 doses for all influenza strains.

The observed seroconversion rates for Season 2 & Season 3 for QIVc recipients by strain were

- A/H1N1: 59.5% [52.55, 66.22] & 74.0% [66.35, 80.75]
- A/H3N2: 19.0% [13.97, 25.02] & 51.9% [43.76, 60.06]
- B/Victoria: 40.0% [33.32, 46.97] & 58.5% [50.23, 66.32]
- B/Yamagata: 49.5% [42.57, 56.49] & 58.4% [50.23, 66.32]

The observed seroconversion rates in the comparator group were between 1.9% and 6.2%.

The differences in the immunological responses measured by HI against Type A/H3N2 in Season 2 compared to Season 3 were observed, with a significantly lower results observed in Season 2. The applicant provided the following explanation for these findings:

> *In recent years, genetic changes in the HA of circulating and vaccine virus strains of A/H3N2 have resulted in the loss of capacity to agglutinate chicken or turkey erythrocytes. This was the case for the A/H3N2 strain used in the vaccine in Season 2 (A/Singapore/GP2050/2015) and thus the HI assay might not have reliably measured the immunogenicity against this virus strain. The HI assay in Season 2 used* (b) (4) *. Under these testing conditions, hemagglutination was predominantly due to neuraminidase (NA) and therefore the assay has measured mostly anti-NA antibodies. Therefore, the HI results observed in Season 2 for the A/H3N2 strains should be considered less reliable. In addition, the use of erythrocytes from different species in Seasons 2 and 3, might also explain the differences in baseline titers across these seasons.*

.

(b) (4) (FAS Immunogenicity Set):

Due to the technical concerns associated with the HI assay with Type A/H3N2, the applicant descriptively evaluated neutralizing antibody titers using (b) (4) assay against each of the 4 strain of virus in the vaccines in Season 2 and 3 in available serum samples. The (b) (4) GMRs in the QIVc group against each strain for Season 2 and Season 3 were as follows: A/H1N2 was 4.93 and 8.42; A/H3N2 was 3.09 and 8.83; B/Victoria 4.75 and 2.83, and B/Yamagata 7.50 and 4.90. The observed GMRs against A/H3N2 were higher for (b) (4) than HI assays, which can be explained by the assay used and strain performance in the HI assay.

> ***Reviewer Comment:***
> HI GMT/GMR, HI seroconversion rates, and (b) (4) GMR were presented descriptively and support the overall primary efficacy analyses that demonstrate QIVc clinical efficacy for the prevention of influenza disease. These immunogenicity data will not be included in the USPI, as the immunogenicity data from Study V130_03 included in the USPI sufficiently inform QIVc immunogenicity in children/adolescents 4 years through 17 years.

6.1.11.5 Dropouts and/or Discontinuations

Missing data were not replaced

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety data surveillance:

- Solicited local injection site and systemic adverse reactions through 7 days postvaccination
  - Solicited (immediate) AEs within 30 minutes postvaccination
- All unsolicited AE through Day 22 for those participants previously vaccinated, and through Day 50 for those participants not previously vaccinated
- SAEs, New Onset Chronic Disease (NOCD), AEs leading to withdrawal, MAAEs (within 30 days after ILI onset) through Day 181 for those previously vaccinated and through Day 209 for those not previously vaccinated

Safety datasets:

- Exposed Set: participants in the All Enrolled Set who received a study vaccination
- Solicited Safety Set (after each vaccination dose): all participants in the Exposed Set who had gone through any assessment of solicited reactions and/or assessment of any use of analgesics/antipyretics
- Unsolicited Safety Set: participants in the Exposed Set who had gone through any AE assessments (participants were not required to report any AEs to be included)
- Overall Safety Set: main population for analysis of safety, includes all participants in Solicited Safety Set and/or Unsolicited Safety Set
    - Participant providing only 30 minutes post-vaccination solicited safety data were also reported separately in a 30-minutes postvaccination safety analysis
    - In case of vaccination error, participants were analyzed as 'treated'
    - Participants randomized in the wrong stratum were reassigned to the correct stratum and were analyzed accordingly
    - Participants who were unblinded during the study were included in all safety sets

6.1.12.2 Overview of Adverse Events

A total of 4514 participants were enrolled and randomized into the study, 4513 were exposed to the study vaccine and included in the Overall Safety Set. The majority (99.9%) of participants were included in the Solicited Safety Set after vaccination-1 and ~33.7% of participants were included in the Solicited Safety Set after vaccination-2, which was consistent with the proportion of participants who reported not receiving a previous vaccination. There were 4 participants (3 in the QIVc group and 1 in the active non-influenza comparator (Menveo) group who were excluded from the Solicited Safety Set because the diary card was not returned. No participants were excluded from the Unsolicited Safety Set.

Solicited Adverse Reactions

The following table provide an overview of solicited adverse reactions (AR) reported during the study for all participants 2 through <18 years, including the number (%) of participants reporting any solicited AR within the 1st 30 minutes postvaccination and during the 7-day reporting period from Day 1 (6hrs) through Day 7 following any vaccination. The comparator for the 1st dose was Menveo, and the comparator for those participants receiving a 2nd dose on Day 29 was saline placebo.

Table 15: Number (%) of Participants Reporting ≥1 Solicited Adverse Reaction After Any Vaccination: Within 30 minutes and From Day 1 (6hrs) through Day 7-Solicited Safety Set

Postvaccination Monitoring Period	**QIVc (N=2255) n (%)**	**Comparator* (N=2254) n (%)**
30 minutes	--	--
-Any Solicited Adverse Reaction	214 (9.5%)	165 (7.3%)
-Local Solicited	202 (9.0%)	157 (7.0%)
-Systemic Solicited	19 (0.8%)	16 (0.7%)
-Use of meds*	5 (0.2%)	3 (0.1%)
Day 1 (6hrs) - Day 7	--	--
-Any Solicited Adverse Reaction	1159 (51.4%)	1096 (48.6%)
-Local Solicited	829 (36.8%)	757 (33.6%)
-Systemic Solicited	707 (31.4%)	688 (30.5%)
-Use of Meds**	195 (8.6%)	164 (7.3%)

Source: Adapted from STN 25408.329, Study V130_12 CSR, Table 12-2. N: total number participants, n: number of participants reporting≥1 solicited AE event. *The non-influenza comparator is Menveo (meningococcal serogroup ACWY conjugate vaccine).

Previously vaccinated participants under 9 years of age and all participants 9 years and older received 1 vaccination with either QIVc or Menveo on Day 1. For participants 2 through 8 years (<9years) who had not previously been vaccinated, then 2 vaccination doses were administered as follows: 1st dose on Day 1 with either QIVc or Menveo; and 2nd dose on Day 29 with either QIVc or saline placebo vaccine. **Use of Meds refers to use of analgesics/antipyretics for prophylaxis or treatment.

The rates of local AR in participants 2 through <18 years occurring within 30 minutes and 7 days of vaccination were higher in the QIVc group (9.0% and 36.8%) versus the comparator group (7.0% and 33.6%), respectively. The rates of systemic AR and use of medications were comparable across groups.

The following two tables provide the proportion (%) of participants across study groups who reported any and grade 3 solicited reactions (AR), including local injection site and systemic AR within the 7 days following vaccinated, based on the Solicited Safety Set. The first table provides the rates of solicited reactions in participants 2 through 8 years and the 2nd table provides the rates of solicited reactions in participants 9 through 17 years.

Table 16: Proportion (%) of Participants 2 through 8 years of Age Reporting Any and Grade 3 Solicited Adverse Reactions Within 7 Days of Any Dose- Solicited Safety Set

	QIVc N=559-1143 Any/Grade 3 %	**Comparator N=562-1142 Any/Grade 3 %**
Local Adverse Reactions[a]	--	--
Tenderness[b]	28.7/1.0	25.4/1.4
Pain	27.9/1.2	20.3/1.6
Erythema	21.3/0.4	23.7/1.1
Induration	14.9/0.2	15.2/0.4
Ecchymosis	10.0/0	7.5/0.1
Systemic Adverse Reactions[c]	--	--
Sleepiness[b]	14.9/0.9	17.6/1.8
Headache	13.8/0.4	11.8/0.5
Fatigue	13.8/0.9	12.7/0.7
Irritability	13.8/0.2	10.8/0.5
Loss of Appetite	10.6/0.5	8.0/0.5
Change of eating habits[b]	9.9/1.0	10.1/0.7
Fever	7.6/0.5	6.1/0.2
Diarrhea	6.5/0.4	6.8/0.6
Arthralgia	5.2/0.4	6.2/0.3
Nausea	5.2/0	4.5/0.7
Vomiting	4.9/0.6	4.1/0.6
Shivering/Chills	4.7/0.7	3.9/0.4
Myalgia	2.9/0.2	4.0/0.3
Use of Meds**	11.0	7.7

Source: Adapted from STN 25408.329, Study V130_12, Am 9, Section 1.14 2 Annotated Draft Labeling Text-Quadrivalent.
Proportion of participant (from 6hrs through 7 days postvaccination) reporting each solicited local adverse reaction or systemic adverse reaction by study vaccine group based on the number of participants contributing any follow up safety information for at least one data value of an individual sign/symptom.

N= number of participants in the Solicited Safety Set for each study group. *The non-influenza comparator is Menveo (meningococcal serogroup ACWY conjugate vaccine). Previously vaccinated participants under 9 years of age and all participants 9 years and older received 1 vaccination with either QIVc or Menveo on Day 1. For participants 2 through 8 years (<9years) who had not previously been vaccinated, then 2 vaccination doses were administered as follows: 1st dose on Day 1 with either QIVc or Menveo; and 2nd dose on Day 29 with either QIVc or saline placebo vaccine. **Use of Meds refers to use of analgesics/antipyretics for prophylaxis or treatment.

[a] Local Adverse Reactions: Grade 3 pain is that which prevents daily activity; Erythema, induration and ecchymosis: any = ≥ 1mm diameter, Grade 3 = > 50 mm diameter for 2 through 5 years and > 100 mm diameter for 6 through 17 years.

[b] Tenderness, change in eating habits, sleepiness, and irritability were collected for participants 2 through 6 years of age only

[c] Systemic Adverse Reactions: Fever: any = ≥ 100.4 F (Oral), Grade 3 = ≥ 102 2 F (Oral); Grade 3 change of eating habits: Missed more than 2 feeds/meals; Grade 3 sleepiness: Sleeps most of the time and is hard to arouse him/her; Grade 3 vomiting: 6 or more times in 24 hours or requires intravenous hydration; Grade 3 diarrhea: 6 or more loose stools in 24 hours or requires intravenous hydration; Grade 3 irritability: unable to console. Grade 3 for all other adverse events is that which prevents daily activity.

For participants 2 years through 8 years, the most frequent solicited reactions reported at higher rates in the QIVc group than the active comparator group (by ≥2%) were injection site tenderness and pain, reported in ~27 - 28% in the QIVc group compared to 25% and 20% in the comparator group, respectively. In addition, headache, irritability, and loss of appetite were reported in 13.8% vs 11.8%, 13.8% vs 10.8%, and 10.6% vs 8.0% of QIVc vs comparator recipients, respectively. The rates of Grade 3 (severe) ARs were comparable across groups and were generally <1% in the QIVc group.

Table 17: Proportion (%) of Participants 9 through 17 years of Age Reporting Any and Grade 3 Solicited Adverse Reactions Within 7 Days of Any Dose- Solicited Safety Set

	QIVc N=1096-1109 Any/Grade 3 %	**Comparator N=1100-1108 Any/Grade 3 %**
Local Adverse Reactions[a]	--	--
Pain	21.7/0.5	18.3/1.0
Erythema	17.2/0	18.7/0.5
Induration	10.5/0.1	11.0/0.2
Ecchymosis	5.0/0	5.2/0
Systemic Adverse Reactions[c]	--	--
Headache	18.1/1.4	17.4/0.6
Fatigue	17.0/1.1	18.2/1.2
Loss of Appetite	8.5/0.5	7.5/0.5
Fever	2.8/0.1	3.0/0.3
Diarrhea	7.4/0.5	8.1/0.3
Arthralgia	7.1/0.4	8.4/0.5
Nausea	6.0/0.2	6.1/0.6
Vomiting	3.0/0.3	3.0/0.4
Shivering/Chills	7.6/0.4	7.6/0.3
Myalgia	6.1/0.5	5.5/0.5
Use of Meds**	6.7	7.1

Source: Adapted from STN 25408.329, Study V130_12, Am 9, Section 1.14 2 Annotated Draft Labeling Text-Quadrivalent.

Proportion of participant (from 6hrs through 7 days postvaccination) reporting each solicited local adverse reaction or systemic adverse reaction by study vaccine group based on the number of participants contributing any follow up safety information for at least one data value of an individual sign/symptom.

N= number of participants in the Solicited Safety Set for each study group. *The non-influenza comparator is Menveo (meningococcal serogroup ACWY conjugate vaccine). Previously vaccinated participants under 9 years of age and all participants 9 years and older received 1 vaccination with either QIVc or Menveo on Day 1. For participants 2 through 8 years (<9years) who had not previously

been vaccinated, then 2 vaccination doses were administered as follows: 1st dose on Day 1 with either QIVc or Menveo; and 2nd dose on Day 29 with either QIVc or saline placebo vaccine. **Use of Meds refers to use of analgesics/antipyretics for prophylaxis or treatment.

[a] Local Adverse Reactions: Grade 3 pain is that which prevents daily activity; Erythema, induration and ecchymosis: any = ≥ 1mm diameter, Grade 3 = > 50 mm diameter for 2 through 5 years and > 100 mm diameter for 6 through 17 years.

[c] Systemic Adverse Reactions: Fever: any = ≥ 100.4 F (Oral), Grade 3 = ≥ 102 2 F (Oral); Grade 3 change of eating habits: Missed more than 2 feeds/meals; Grade 3 sleepiness: Sleeps most of the time and is hard to arouse him/her; Grade 3 vomiting: 6 or more times in 24 hours or requires intravenous hydration; Grade 3 diarrhea: 6 or more loose stools in 24 hours or requires intravenous hydration; Grade 3 irritability: unable to console. Grade 3 for all other adverse events is that which prevents daily activity.

For participants 9 years through 17 years, the most frequent solicited reaction reported at higher rates in the QIVc group than the active comparator group (by ≥2%) were injection site pain, reported in ~22% (<1% Grade 3) in the QIVc group compared to 18% (1% Grade 3) in the comparator group. In addition, headache, irritability, and loss of appetite were reported in 13.8% vs 11.8%, 13.8% vs 10.8%, and 10.6% vs 8.0% of QIVc vs comparator recipients, respectively. All other reactions were reported at comparable rates across groups.

Solicited AR-Subgroup Analyses: Age

Within 30 minutes of vaccination, the rates of AR across study groups for different age sub-cohorts (2-5 years; 6–8 years; 9- 17years) were generally similar. However, induration was reported at slightly higher rates in children 2-5 years (1.4% QIVc vs 5% comparator) compared to 9-17 years (1.2% QIVc vs 0.6% comparator) but the number of participants reporting these events across groups were low (3 to13 participants). The reports of pain within 30 minutes of vaccination were higher in children 6 – 8 years (8% QIVc vs 4.9% comparator) than in participants 9-17 years (4.7% QIVc vs 3.8% comparator) with slightly higher number of participants reporting these events (28 to 45 participants).

By age sub-cohorts the rates of solicited AR from 6 hours through 7 days after any vaccination were generally similar, and included the following:

- 2 through 5 years
    - Local: 39.1% QIVc vs 37.7% comparator
    - Systemic: 31.4% QIVc vs 29.7% comparator
- 6 through 8 years
    - Local: 41.7% QIVc vs 35.3% comparator
    - Systemic: 29.6% QIVc vs 27.2% comparator
- 9 through 17 years
    - Local: 33.0% QIVc vs 30.6% comparator
    - Systemic: 32.2% QIVc vs 32.7% comparator

The proportion of participants across age sub-cohorts reporting other indicators of reactogenicity (body temperature measurements, use of analgesics/antipyretics) were generally similar, with slightly higher rates of anti-pyretic/analgesic preventive and treatment medications use in the 2-5 years age sub-cohort (7-8% QIVc vs 6% comparator) compared to the 9 to 17 years age sub-cohort (4-5% QIVc vs 4-5% comparator group).

Solicited AR-Subgroup Analyses: Race, Sex, and Prior Vaccination History

The reported rates of solicited local AR from 6 hours through 7 days post-vaccination were higher in White participants (51.8% QIVc vs 48.5% comparator) than in Asian participants (20.7% QIVc vs 17.6% comparator). There were no significant differences in the reported rates of solicited AR based on sex. The proportion of participants reporting local AR were lower in those previously vaccinated compared to those not previously vaccinated.

- rates of local tenderness in participants 2 through 5 years
    - previously vaccinated: 19.1% QIVc vs 21.0% comparator

    - not previously vaccinated: 33.6% QIVc vs 27.5% comparator
- rates of local pain in participants 6 through 8 years
    - previously vaccinated: 24.0% QIVc vs 14.6% comparator
    - not previously vaccinated: 29.8% vs 23.2% comparator

Unsolicited Adverse Events

The following table provides an overview of unsolicited adverse events, including unsolicited AEs reported through Day 22 following the 1st dose and through Day 50 following the 2nd dose. Also listed are the rates across groups of SAEs, AEs leading to study withdrawal, MAAEs, NOCD, and deaths reported through the end of the respective influenza season or through Day 181 (or Day 209 for those receiving 2 doses). This table also includes the proportion of participants reporting AEs or SAEs considered related to study vaccination and AEs by severity.

Table 18: Number (%) of Participants Reporting ≥1 Unsolicited AE and All Other AE Categories- As Treated-Overall Safety Set

Postvaccination Monitoring Period	**QIVc (N=2258) n (%)**	**Comparator* (N=2255) n (%)**
Day 1- Day 22/Day 50**	--	--
Any AE	633 (28.0%)	630 (27.9%)
-Mild	550 (24.4%)	555 (24.6%)
-Moderate	109 (4.8%)	101 (4.5%)
-Severity	11 (0.5%)	11 (0.5%)
Related AE	97 (4.3%)	89 (3.9%)
SAE^	25 (1.1%)	30 (1.3%)
Related SAE^	0	0
AE leading to Study Withdrawal^	0	0
MAAE^	614 (27.2%)	679 (30.1%)
NOCD^	9 (0.4%)	11 (0.5%)
Death^	0	1 (<0.1%)

Source: Adapted from STN 25408.329, Study V130_12 CSR, Table 12-3. N: total number participants, n: number of participants reporting≥1 AE event by category. *The non-influenza comparator is Menveo (meningococcal serogroup ACWY conjugate vaccine). Previously vaccinated participants under 9 years of age and all participants 9 years and older received 1 vaccination with either QIVc or Menveo on Day 1. For participants 2 through 8 years (<9years) who had not previously been vaccinated, then 2 vaccination doses were administered as follows: 1st dose on Day 1 with either QIVc or Menveo; and 2nd dose on Day 29 with either QIVc or saline placebo vaccine. ** Day 22 for all previously vaccinated participants (receiving a single dose) and Day 50 for all 'not previously vaccinated' participants (receiving 2 doses). ^ SAEs, AEs leading to study withdrawal, MAAEs, NOCD and deaths reported through the end of the respective influenza season or through Day 181 (or Day 209 for those receiving 2 doses).

The rates of unsolicited non-serious AE following study vaccinations were comparable across study groups, including those graded severe in intensity (0.5% in both groups). Across groups the rates of related AEs were ~4%, SAEs were ~1%, and NOCD were $\leq$ 0.5%, while MAEEs were lower in the QIVc group (27%) than the comparator group (30%). There were no deaths in QIVc recipients, one death in comparator vaccine recipients, and no SAEs that were considered related to study vaccinations.

The most frequently AEs occurring through Day 22 (if received 1 dose) or Day 50 (if received 2 doses) were classified under the Infections and Infestations system organ class-SOC (15.7% QIVc vs 15.8% comparator), of which the most frequently reported preferred terms (PT) were upper respiratory tract infections (4.5% QIVc vs 4.1% comparator) and rhinitis (3.4% QIVc vs 3.8% comparator). The 2nd most frequently reported SOC was General Disorders and Administration Site Conditions SOC (11.8% QIVc vs 11.4% comparator), the most frequently

reported PT was Influenza like illness- ILI (9.4% QIVc vs 8.9% comparator), of which was also the most frequently reported possibly related unsolicited AE by PT was ILI across study groups (1.1% QIVc vs 0.9% comparator).

Unsolicited AEs-Subgroup Analyses: Age, Race, Sex, and Vaccination History
The reported rates of unsolicited AEs were higher in participants 2 through 8 years (37.7% QIVc vs 39.5% comparator) than participants 9 through 17 years (18.1% QIVc vs 16.0% comparator), and most events were graded mild/moderate in severity. Events considered related to vaccination were also higher in the younger age cohort (5.9% QIVc vs 4.4%) compared to the older age cohort (2.6% QIVc, vs 3.5% comparator). The rates of SAEs and NOCD in both age sub-cohorts were low across groups. There was one death in the 2 to 8 years age sub-cohort in the comparator group. There was no difference observed in the rates of unsolicited AEs based on race or sex. The rates of unsolicited AEs were higher in participants not previously vaccinated (43.9% QIVc vs 45.6% comparator) than in participants previously vaccinated (19.8% QIVc vs 18.8% comparator).

6.1.12.3 Deaths

There was one reported death during the study in the comparator group for participant # (b) (6) . The participant was an 8 year old female at the time of enrollment who had SAE of diabetic ketoacidosis and cerebral edema on Day 220 (119 days after the last vaccination) who died one day later on Day 221. The death was not considered by the study investigator and this reviewer as related to study vaccination.

6.1.12.4 Nonfatal Serious Adverse Events

There were 25 SAEs in QIVc recipients and 30 SAEs in comparator vaccine recipients, none of which were considered by the study investigator and this reviewer as related to study vaccination. During the treatment period (Day 22/Day 50 postvaccination), there were 14 SAEs reported, 7 in each group. Of the 7 SAEs in the QIVc group, 3 were in the Infections and Infestations SOC- including pneumonia, pharyngitis, and pneumonia mycoplasma. The other SAEs included a clavicle fracture, hand fracture, multiple fractures, and gastritis.

6.1.12.5 Adverse Events of Special Interest (AESI)

There were not protocol specified AESI included in the study design.

6.1.12.6 Clinical Test Results

6.1.12.7 Dropouts and/or Discontinuations

Table 19: Study Disposition V130_12

Population	**QIVc (N=2258) X (%)**	**Comparator (N=2256) X (%)**
Enrolled	2258 (100%)	2256 (100%)
Vaccinated	2258 (100%)	2255 (99.96%)
Completed Study	2249 (99.6%)	2247 (99.6%)

Withdrawal due to	--	--
Voluntary W/d	3 (0.13%)	3 (0.13%)
Lost to F/up	5 (0.22)	2 (0.09%)
Admin. Reason	0	0
Protocol violation	0	0
AE/SAE	0	0
Death	0	1

Source: Adapted from STN 25408.329, Study V130_12 CSR, Table 10-1.

Across study groups, the rates of participant discontinuations were low, and comparable across groups. There were no reports of AEs resulting in study discontinuation.

6.1.13 Study Summary and Conclusions

Accelerated approval of QIVc for use in US children 4 to <18 years of age was approved by FDA in May 2016. Study 130_12 safety and effectiveness data support granting "traditional" approval, thereby fulfilling the requirement to conduct a post-marketing study to verify and describe the clinical benefit of QIVc in children 4 years through 17 years (<18 years). The design of the study was revised to include children 2 through 3 years (<4 years) under the IND to align with other regulatory agencies. Vaccine efficacy of QIVc against influenza disease compared to a non-influenza active comparator in participants 2 years through 17 years of age was 54.6% and the lower limit of the 2-sided 95% CI around the VE point estimate was 45.7 (success criterion: LL >20%). The safety data from this study supports QIVc use in children 2 years through 17 years of age. The safety and effectiveness data in ~200 QIVc vaccine recipients 2 through 3 years of age supports its use in this age cohort, therefore constitute a pediatric assessment to address PREA requirements for children 2 to <4 years of age. We therefore consider PREA PMR #2 to be partially fulfilled (for the age group 2 years to < 4 years of age) based on the study V130 12 results.

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

The USPI was revised as part of this clinical efficacy supplement to include updates to Section 8 of both the QIVc and TIVc to comply with the Pregnancy and Labeling Labelling Rule (PLLR) to ensure that the information provided in both reflect the most current knowledge. Because the pregnancy registry for QIVc was completed and the applicant claims that no meaningful data were currently available to revise the QIVc USPI. For TIVc, the pregnancy registry was closed due to minimal enrollment, language pertaining to it in Section 8.1 was removed.

9.1.2 Use During Lactation

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

9.1.3 Pediatric Use and PREA Considerations

The purpose of this clinical efficacy supplement was to provide study V130_12 results to fulfill AA post-marketing study requirements (PMR) for both Flucelvax QIVc and Flucelvax (trivalent) in children 4 to <18 years of age. Study V130_12 was designed to evaluate the efficacy, safety and immunogenicity of Flucelvax QIVc compared to a non-influenza comparator vaccine. The Applicant submitted an IND amendment to enroll children as young at 2 years of age in the study, mainly to fulfill EMA pediatric requirements; the IND clinical reviewers agreed with the study design changes.

Following review of study V130_12 safety and clinical endpoint efficacy data, the sBLA Review Team concluded that the results also support safety and effectiveness for use of QIVc in children 2 years to <4 years of age. As such, the study results contained in this sBLA constitute an assessment for children 2 years to <4 years of age. An assessment in children 2 to <4 years of age for both Flucelvax QIV and Flucelvax (TIV) was planned to be based on safety and immunogenicity data from a PREA PMR study, V130_10 [see PMR #2 Flucelvax Quadrivalent Influenza Vaccine (STN 125408/127) approval letter dated May 23, 2016 and PMR #2 Flucelvax (STN 125408/101) approval letter dated May 23, 2016]. Enrollment in study V130_10 also included infants/toddlers 6 months to <2 years, and the results of this study were submitted in efficacy supplement STN 125408/(b) (4), which is currently under review. We therefore consider PREA PMR #2 to be partially fulfilled (for the age group 2 years to < 4 years of age) based on the study V130 12 results. This pediatric assessment in children 2 years through <4 years was presented to PeRC on January 19, 2021. The assessment for ages 6 months to <2 years, based on study V130_10 results, will be presented to PeRC under STN 125408/(b) (4).

> ***Reviewer Comment:***
> The submitted safety and clinical endpoint efficacy data in children 2 years through <4 years support the safety and effectiveness of QIVc and as such constitute a pediatric assessment for this age group. Also, the safety and clinical efficacy data support full approval of Flucelvax Quadrivalent Influenza Vaccine for the proposed indication in children 4 years through 17 years of age (<18 years). The package insert is appropriately labeled for the pediatric population 2 to <18 years of age.

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 ~2687 individuals 65 years of age and older in clinical studies.

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

10. CONCLUSIONS

The safety and efficacy data of in this clinical efficacy supplement support the use of QIVc (and TIVc) in children 2 years through 17 years of age.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 20: Risk-Benefit Assessment of QIVc in Person 2 years through 17 years.

Decision Factor		Conclusions and Reasons
Analysis of Condition	• Influenza typically causes annual epidemics during the late fall through the early spring and can cause pandemics. • Severity of disease (rates of hospitalization and death) is worst in the elderly, young children, and individuals with medical conditions that place them at increased risk for complications. • Influenza infects 5-20% of the population each year with a wide range of severity, including up to 200,000 hospitalizations and 3,000 to 44,000 death in the US annuals.	• Considerable morbidity and mortality is associated with yearly influenza epidemics. Influenza vaccines are the most effective way of preventing morbidity and mortality due to influenza.
Unmet Medical Need	• The majority of inactivated influenza vaccines and one live attenuated influenza vaccine are licensed for use in the US are produced in embryonated hen eggs. The use of eggs in manufacture of these influenza vaccine results in a reliance of egg supply, long production timelines, difficulty with scaling up production in an emergency, and inclusion of egg proteins in vaccines.	• QIVc is derived is the 1st cell derived influenza vaccine to be licensed in the US. • It is manufactured in MDCK cells instead of eggs, and as result production scale up is quicker. It contains unmeasurable amounts of egg proteins, and therefore may be appropriate for use in children with egg allergies.
Clinical Benefit	• Vaccine efficacy of QIVc compared to an active non-influenza comparator was demonstrated in Study V130_12 included in this clinical efficacy supplement evaluating over 4514 randomized participants 2 to <18 years of age: 2258 in QIVc arm and 2256 in comparator-Menveo arm. • Vaccine efficacy of QIVc against influenza disease compared to a non-influenza active comparator in participants 2 years through 17 years of age was 54.6% and the lower limit of the 2-sided 95% CI around the VE point estimate was 45.7% (success criterion: LL >20%).	• Clear evidence of clinical benefit was demonstrated in a clinical endpoint efficacy trial.
Risk	• The most substantial risks of vaccination with QIVc includes solicited adverse reactions: the most frequent solicited reactions reported were injection site tenderness/pain, headache, irritability, and loss of appetite. • There were SAEs that were considered by the study investigator or this reviewer to be related to vaccination	• Most solicited reactions were mild/moderate in severity and self-limiting.
Risk Management	• The most frequently reported risks of vaccination with Flucelvax QIVc were reactions at the injection site that were typically mild and resolved within days. These will be described • in the package insert.	• The risks of QIVc are adequately addressed in the package insert. The PVP is unchanged.

11.2 Risk-Benefit Summary and Assessment

Data submitted to the clinical efficacy sBLA establish the safety and efficacy of QIVc in individuals 2 years through 17 years of age. The risk associated with QIVc vaccination appear to be minimal based on the submitted data. The clinical efficacy data support a favorable risk-benefit profile.

11.3 Discussion of Regulatory Options

The applicant is seeking full approval of QIVc (and TIVc) for use in children 2 to <18 years of age. The indication remains unchanged:

> *For active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.*

11.4 Recommendations on Regulatory Actions

After reviewing the V130_12 report, I agree that the safety and effectiveness of QIVc in children 2 years through 17 years for the prevention of influenza disease cause by influenza virus subtypes A and type B contained in the vaccine supports granting "traditional" approval for children 4 to <18 years of age, which fulfill the regulatory requirement for AA, and "traditional" approval in children 2 to <4 years of age, which fulfill the PREA requirements for an assessment in children 2 to <4 years of age.

Revocation of Flucelvax (TIVc)
On January 29, 2021, Seqirus submitted a Product Correspondence (STN 125408/361) to request a voluntary revocation of the Flucelvax (TIVc) product. CBER management determined that a revocation of the trivalent formulation would be issued in the same timeframe as the final action for this supplement. As such, Seqirus will be released from any outstanding PMRs for the trivalent formulation, including the accelerated approval PMR under review in this supplement (Study V130_12) and PREA PMR #2 (Study V130_10, for children 6 months to <4 yrs of age. Approval of Flucelvax for children 2 yrs of age and above will therefore apply only to the quadrivalent product (QIVc). No labeling update will be required for the trivalent formulation for this or future supplements

11.5 Labeling Review and Recommendations

With this clinical efficacy supplement, the information about the safety and efficacy of QIVc in children 2 years through 17 years was added to the QIVc label and the TIVc label. Section 6.1 was revised to describe the study design for Study V130_12, as well as safety findings. Section 14.2 of the USPI was revised to include efficacy data. I agree with the final draft labeling submitted to sBLA 125408/329.

11.6 Recommendations on Postmarketing Actions

The applicant plans to follow the current routine pharmacovigilance plan, as no new or potential risks were identified.