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Division / Office	OVR
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Priority Review	No
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Review Completion Date / Stamped Date	
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Applicant	Seqirus, Inc.
Established Name	Quadrivalent inactivated vaccine, cell-derived (QIVc)
(Proposed) Trade Name	Flucelvax
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Influenza vaccine strains: Season 1 [Southern Hemisphere 2017]: Type A/Singapore/GP1908/2015 IVR-180 (H1N1); A/HongKong/4801/2014 (H3N2); B/Utah/9/2014 (B Yamagata); B/HongKong/259/2010 (B Victoria). Season 2 [Northern Hemisphere 2017-2018]: A/Singapore/GP1908/2015 IVR-180 (H1N1); A/Singapore/GP2050/2015 (H3N2); B/Utah/9/2014 (B Yamagata); B/HongKong/259/2010 (B Victoria). Season 3 [Northern Hemisphere 2018-2019]: A/Singapore/GP1908/2015 IVR-180 (H1N1); A/North Carolina 04/2016 (H3N2); B/Singapore/INFTT-16-06 10/2016 (B Yamagata); B/Iowa/06/2017 (B Victoria).
Dosage Form(s) and Route(s) of Administration	Suspension for intramuscular (IM) injection supplied in 0.5-mL single-dose pre-filled syringes
Dosing Regimen	For 2 through 8 years of age, one or two doses, 0.5 mL each (If 2 doses, administer at least one month apart); for 9 years of age or older, one dose, 0.5 mL
Indication(s) and Intended Population(s)	For use in persons 2 years of age or older for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine

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GLOSSARY

AE	Adverse Event
aVE	Absolute Vaccine Efficacy
BIMO	Bioresearch Monitoring
CBER	Center for Biologics Evaluation, Research and Review
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CSR	Clinical Study Report
DMC	Data Monitoring Committee
FAS	Full Analysis Set
FDA	Food and Drug Administration
GMT/R	Geometric Mean Titer/Ratio
HA	hemagglutinin
HI	hemagglutination inhibition
HR	Hazard Ratio
ILI	Influenza-like Illness
IM	Intramuscular
LL	Lower Limit
MenACWY	Meningococcal (Groups A, C, W-135, Y) Conjugate Vaccine
MDCK	Madin-Darby Canine Kidney
NH	Northern Hemisphere
NODC	New Onset of Chronic Disease
PPS	Per-protocol Set
QIVc	Quadrivalent Cell-based Influenza Vaccine
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Seroconversion
sBLA	Supplemental Biologic Licensing Application
SH	Southern Hemisphere
TIVc	Trivalent Cell-based Influenza Vaccine

1. Executive Summary

The applicant, Seqirus, submitted this supplemental Biologics Licensing Application (sBLA) in support of full licensure of a quadrivalent cell-based influenza vaccine (QIVc) in the 2 to <18 years of age group, after an initial accelerated approval in the 4 to <18 years of age group in 2016. This submission contains the results of Study V130_12, a Phase 3/4, stratified, randomized, observer blind, multicenter study to evaluate efficacy, safety and immunogenicity of the QIVc compared to non-influenza comparator (Menveo or Menveo + placebo) in subjects 2 to <18 years of age.

Overall, V130_12 demonstrated a successful absolute vaccine efficacy (aVE) of 54.6% (95% CI: 45.7%, 62.1%) in the 2 to <18-year-old age range and a comparable safety profile to that of the conjugate quadrivalent meningococcal vaccine comparator. Key findings are summarized below.

- In the pediatric study of the trivalent cell-based vaccine supporting the accelerated approval, the strain A/H3N2 did not demonstrate non-inferiority to an egg-based vaccine. In this study, aVE estimates (95% CI) for the A/H1N1, A/H3N2, and B strains were 80.7% (69.2%, 87.9%), 42.1% (20.3%, 57.9%), and 47.6% (31.4%, 60.0%), respectively.
- During conduct of the study, the protocol was changed to extend the previously specified age range of 3 to <18 years to 2 to <18 years. This extends the accelerated approval age range to include 2 to <4 years. Overall aVE estimates indicate the vaccine is effective in the 2 to <4 age group [aVE (95% CI): 62.7% (38.1%, 77.5%), versus the 4 to <18-year olds aVE (95% CI): 53.3% (43.4%, 61.5%)].
- The study was extended to include a third season for reasons not pre-specified in the protocol. External justification included counteracting an over-enrollment in the Philippines in Season 1 and to recruit more 2 to 3-year olds to accommodate the increased age range. Efficacy in the Philippines was comparable to other countries, and efficacy in the younger age group was reasonable (see previous bullet).

The safety profile is similar to that of Menveo, and only slightly more reactogenic than the placebo comparison (i.e., the comparison after the second dose of the Flucelvax-Flucelvax arm to the Menveo-placebo arm in previously unvaccinated 2 to <9-year olds). There are no major safety concerns from the statistical perspective.

Overall, efficacy and safety results support full approval of the QIVc, Quadrivalent Flucelvax, in the 2 to <18-year-old age range.

2. Clinical and Regulatory Background

Flucelvax is a purified, inactivated, trivalent subunit influenza vaccine manufactured in a Madin-Darby Canine Kidney (MDCK) cell line (abbreviated as TIVc). The TIVc was approved by the FDA on November 20, 2012, for use in the prevention of influenza in adults 18 years of age and older. The applicant subsequently submitted a supplement to this BLA to extend the age range of TIVc to 4 years of age and older. However, the pivotal immunogenicity trial in this population (V58P12) failed to demonstrate immunologic non-inferiority of Flucelvax compared to Fluvirin with respect to the A/H3N2 influenza strain and a complete response letter was issued on September 17, 2015.

The applicant then submitted a major amendment seeking traditional approval of a quadrivalent version of Flucevax (Flucelvax Quadrivalent, abbreviated QIVc) in adults (18 years of age and older) and accelerated approval in the pediatric population age 4 years and above. This application was approved on May 23, 2016, and the approval was extended to TIVc in age 4 years and above at the same time.

This BLA supplement is submitted in fulfillment of the post-marketing accelerated approval requirement to conduct a study to evaluate the efficacy, safety and immunogenicity of the QIVc.

2.1 Disease or Health-Related Condition(s) Studied

Influenza in children from 2 to < 18 years of age.

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

N/A

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

QIVc was approved for use in individuals 4 and older in the US since May 2016 and in individuals aged 9 years and older in Europe since December 2018 and Canada since November 2019.

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

N/A

2.6 Other Relevant Background Information

N/A

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission is adequate for conducting a complete statistical review.

3.2 Compliance with Good Clinical Practices and Data Integrity

Per the applicant, during review of the antigenic typing results, it was discovered that 19 of the 22 H3N2 culture-positive samples from Season 2 had been tested with (b) (4) from Season 1. It was decided that these had to be retested, including a new lab data transfer and update of the relevant tables and listings. The results presented represent the correctly tested samples. Please see the BIMO review for a thorough review of data integrity.

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

Please refer to the reviews of the corresponding discipline reviewers (CMC, assay validation, nonclinical pharmacology/toxicology, clinical, pharmacovigilance).

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

5.1 Review Strategy

This review is focused on one clinical trial, V130_12.

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

The main study was submitted in STN 125408/329.0, with the following subsections considered in this review.

- Module 2.5. Clinical Overview
- Module 2.7.3 Summary of Clinical Efficacy
- Module 2.7.4 Summary of Clinical Safety
- Module 5.3.5.1. Study V130_12 Clinical Study Report

Analysis programs were submitted under STN 125408/329.2 and were considered in the verification of the study results.

5.3 Table of Studies/Clinical Trials

Table 1: Summary of the study under review in this application

Study Number/ Years	Geographic Locations	Objective(s) of the Study	Study Design and Type of Control	Test Product (s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled	Population
V130_12/ 2017 2017/2018 2018/2019	Australia Estonia Finland Lithuania Philippines Poland Spain Thailand	Safety; Immunogenicity; Efficacy	Phase 3/4 Observer-blind, randomized, controlled (non-influenza vaccine comparator)	QIVc Menveo® Meningococcal Conjugate Vaccine 1 or 2 vaccinations of 0.5 mL, 4 weeks apart; IM	Total 4,514 2258 in the QIVc group and 2256 in the control group	Healthy subjects aged 2 to <18 years

Abbreviations: IM = intramuscular; QIVc = Cell culture-derived quadrivalent influenza vaccine

Source: STN 125408/329/0, Module 5.2, Tabular Listing of All Clinical Studies

5.4 Consultations

N/A

5.5 Literature Reviewed (if applicable)

N/A

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study V130_12

A Phase 3/4, 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.

6.1.1 Objectives (Primary, Secondary, etc)

Primary Efficacy Objective:

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 subjects 2 to <18 years of age.

Co-Primary Efficacy Objective:

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 subjects 3 to <18 years of age.

Reviewer comment: This protocol was revised several times while the study was being conducted. The co-primary efficacy objective listed was originally proposed as a single primary objective. During the study, the applicant requested to change the age range down to 2 years of age to accommodate approval requirements of other regulatory authorities. CBER suggested an additional objective to demonstrate aVE > 0% in the 2 to <4-year-old age range, but the applicant declined and cited feasibility difficulties. As such, it was not clear that the intent was driven by external motivations, so CBER requested the co-primary efficacy objective be included. The applicant is seeking approval for age 2 and above.

Secondary Efficacy Objectives:

1. 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 cohorts 2 to <9 years of age, 4 to <18 years of age, and 9 to <18 years of age.

The following secondary objectives were evaluated in 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.

To demonstrate aVE of QIVc versus a non-influenza comparator determined by the first occurrence of:

2. RT-PCR confirmed influenza due to any influenza Type A and B strain.
3. Culture-confirmed influenza due to any influenza Type A and B strain.
4. Culture-confirmed influenza caused by influenza strains antigenically matched to the strains selected for the seasonal vaccine.

Secondary Immunogenicity Objective:

To characterize the immunogenicity of QIVc by hemagglutination inhibition (HI) assay 3 weeks after the last vaccination in a subset of subjects in the age cohort 2 to <9 years of age.

Secondary Safety Objective:

To assess the safety and tolerability of QIVc.

6.1.2 Design Overview

The study was designed as a Phase 3/4, stratified, randomized, observer-blind, multicenter study to evaluate the efficacy, safety, and immunogenicity of QIVc compared to a non-influenza comparator vaccine in healthy male and female subjects 2 to <18 years of age. Randomized subjects were stratified in 2 age cohorts: 2 to <9 years of age and 9 to <18 years of age. Subjects between 2 to <9 years of age were further stratified by previous influenza vaccine status, where “previously vaccinated” was defined as having received 2 or more doses of seasonal influenza vaccine before or during the last influenza season (not necessarily in the same influenza season). “Previously vaccinated” subjects received 1 vaccination, and “not previously vaccinated” subjects received 2 vaccinations approximately 28 days apart. A subset of subjects was selected to participate in an assessment of immunogenicity, balanced by vaccination status and assigned vaccination allocation.

6.1.3 Population

Healthy subjects aged 2 to <18 years of age.

6.1.4 Study Treatments or Agents Mandated by the Protocol

A 0.5 mL pre-filled syringe dose of QIVc contains nominally 15 µg of hemagglutinin (HA) of each of the 2 influenza type A strains and each of the 2 influenza type B strains for a total of 60 µg of HA in the vaccine.

This 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]). Strain composition was based on recommendations by the WHO for the respective season. See Table 2 for vaccine lot information and strain composition of the investigational QIVc and Table 3 for the lot information on the Menveo comparator and the placebo.

Table 2: Lot numbers, expiry dates, and strain composition for the investigational QIVc

Study Vaccine	Lot Numbers	Expiry Date	Strain composition
Season 1 - QIVc SH 2017	192679	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 - QIVc NH 2017/2018	195215	04/2018	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 - QIVc NH 2018/2019	252661	05/2019	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).

Source: STN 125408/329/0, VI30_12 CSR, Table 9-1, p. 49 and Table 9-2, p. 50

Table 3: Lot numbers and expiry dates for the comparator Menveo and placebo

Study Vaccine	Season	Lot Numbers	Expiry Date
Meningococcal (Group ACWY) Conjugate Vaccine (Menveo)	1	M16039	10/2017
Meningococcal (Group ACWY) Conjugate Vaccine (Menveo)	2	M16106	07/2018
Meningococcal (Group ACWY) Conjugate Vaccine (Menveo)	3	M17043	04/2020
Placebo (Sodium Chloride Injection 0.9% w/v)	1	16381013	08/2019
Placebo (Sodium Chloride Injection 0.9% w/v)	2	17203011	04/2020
Placebo (Sodium Chloride Injection 0.9% w/v)	3	18096011	02/2021

Source: STN 125408/329/0, VI30_12 CSR, Table 9-2, p. 50

6.1.6 Sites and Centers

This study was conducted at 39 centers in 8 countries: 2 in Australia, 5 in Estonia, 10 in Finland, 6 in Lithuania, 7 in the Philippines, 6 in Poland, 1 in Spain, and 2 in Thailand.

6.1.7 Surveillance/Monitoring

Please refer to the clinical review.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoints

The primary and co-primary efficacy endpoints were defined as 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 occurring more than 14 days after the last vaccination until the end of the influenza season.

An influenza case was defined as RT-PCR-confirmed or culture-confirmed influenza in a subject who met the Centers for Disease Control and Prevention (CDC) criteria for influenza-like illness (ILI) modified for young children (e.g. fever, along with any of the following symptoms: cough, sore throat, nasal congestion, or rhinorrhea).

Efficacy of the QIVc was demonstrated in the 2 to <18-year age range if the lower limit (LL) of the 2-sided 95% confidence interval (CI) for aVE was above 20% (primary objective). Efficacy of the QIVc was demonstrated in the 3 to <18-year age range if the lower limit (LL) of the 2-sided 95% confidence interval (CI) for aVE was above 30% (co-primary objective).

Secondary Efficacy Endpoints

The first secondary efficacy endpoint uses the same endpoint definition of the primary endpoints. The remaining secondary efficacy endpoints were similarly defined as the primary efficacy endpoint, restricting the definition of an influenza case to RT-PCR-confirmed only (Secondary Objective 2), culture-confirmed only (Secondary Objective 3), and culture-confirmed influenza due to influenza Type A or B strain antigenically matched to the strains selected for the seasonal vaccine (Secondary Objective 4).

Secondary Immunogenicity Endpoints

The immunogenicity of study vaccines was assessed 21 days after the last vaccine administration by the HI assay for the 4 viral strains included in the vaccines. Endpoints of interest included geometric mean titers (GMTs), percentage of subjects achieving seroconversion (defined as a prevaccination HI titer <1:10 and a postvaccination HI titer \geq 1:40 or a prevaccination HI titer \geq 1:10 and a \geq 4-fold increase in postvaccination HI titer), geometric mean ratio (GMR) of Day 22/Day 1 (all previously vaccinated subjects receiving a single vaccine dose) or Day 29/Day 1 and Day 50/Day 1 (all subjects not previously vaccinated subjects receiving 2 doses), and percentage of subjects with HI titer \geq 1:40.

Secondary Safety Endpoints:

Safety of the study vaccines was assessed in terms of percentages of subjects exposed to study vaccine with reported 1) solicited local and systemic AEs; 2) unsolicited AEs; 3) SAEs and/or AEs leading to withdrawal from vaccination and/or the study, ILIs, and new onset of chronic diseases (NOCDs); and 4) medically-attended AEs.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Subjects were randomized 1:1, using stratification factors of age group and previous vaccination. There was a goal to enroll enough subjects to adequately estimate VE in the relevant subgroups (e.g. 50% aged 9 to <18 years and 50% aged 2 to <9 years, and an approximate ratio of 2:1 for “not previously vaccinated” versus “previously vaccinated”).

For the primary objective, the hypotheses for aVE are $H_0: aVE \leq 20\%$ vs. $H_A: aVE > 20\%$, and for the co-primary objective, the hypotheses are $H_0: aVE \leq 30\%$ vs. $H_A: aVE > 30\%$.

Reviewer comment: CBER agreed to the lower bound success criterion of 30% prior to analysis, while the acceptability of a 20% lower bound was not discussed prior to analysis.

For both objectives, aVE is calculated as $1 - HR$, where HR is estimated by a proportional hazards regression model with treatment effect as a fixed effect, and the stratifying covariates as random effects: $h_i(t) = h_0(t) \exp(\beta^*X + b^T Z)$. Here, for a sequentially tested primary objective i ($i=1,2$), t is time to influenza, β is the treatment group effect indicated by X , b is random effect (assumed as a multivariable random gaussian variable with zero mean and diagonal covariance matrix), and Z is the random effect covariate (reflecting randomization stratum age, previous vaccination history, season, and country). For random effects, a crosstabulation (crosstab) of all covariates defined a single group (e.g. age 2 to <9 years, previously vaccinated, Australia, Season 1 is one group), and thus each possible crosstab group was allowed a different baseline hazard function. The success criteria were evaluated using model-based 95% confidence intervals.

Should the sponsor or DMC have called for an interim analysis, the plan was to adjust alpha using an alpha-spending function. However, no interim analysis was done.

Study vaccines were administered in observer-blind fashion. Unblinded personnel administered the vaccine. After vaccination, safety assessments and study related procedures and monitoring thereof must be performed by blinded team members.

The following analysis populations were considered:

- Full Analysis Sets (FAS): FAS Efficacy included all enrolled subjects who received at least one dose of the study vaccine and were evaluated for efficacy from 14 days after the last vaccination. FAS Immunogenicity included all enrolled subjects who received at least one dose of the study vaccine and provided evaluable serum samples at both baseline and after the last vaccination. In case of vaccination error, subjects in the FAS were analyzed “as randomized”. FAS were further restricted for purpose (e.g. correct age range or strain/assay type specific).
- Per Protocol Set (PPS) included all subjects in the FAS set who correctly received the vaccine and had no major protocol deviations such as vaccination not according to protocol, took an excluded medication, or key study procedures not performed or performed out of window.
- Safety Set included all subjects who were assessed for relevant safety data. The safety set population was analyzed “as treated.”

Missing data were not imputed. Missing values were considered by the applicant as completely missing at random and the analysis was complete case only.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 4514 subjects 2 to <18 years of age were enrolled and randomized into the study to receive QIVc or comparator vaccine. Loss to follow-up was balanced across arm and was minimal (<1% in each arm). An overview of analysis sets is in Table 4.

Table 4: Overview of Efficacy and Immunogenicity Sets Analyzed – As Randomized

	QIVc N=2258 n (%)	Comparator N=2256 n (%)	Total N=4514 n (%)
All Enrolled Set	2258 (100)	2256 (100)	4514 (100)
All Exposed Set	2258 (100)	2255 (100)	4513 (100)
FAS, Efficacy, 2 to <18 years	2257 (100)	2252 (100)	4509 (100)
PPS, Efficacy, 2 to <18 years	2219 (98)	2209 (98)	4428 (98)
FAS, Immunogenicity, 2 to <9 years	364 (16)	357 (16)	721 (16)
PPS, Immunogenicity, 2 to <9 years	349 (15)	339 (15)	688 (15)

Source: sBLA 125408/329, V130_12 CSR, p. 112, Table 10-3.

6.1.10.1.1 Demographics

Demographics were generally well-balanced across study arms. Additionally, age groups were well-balanced with approximately 51% aged 2 to <9 years and 49% aged 9 to <18

years, for both arms. There were approximately 10% of the subjects aged 2 to <4 years, which is an extension of the age group that was approved under accelerated approval.

There were 51% male to 49% female in both arms, and approximately 49% Asian and 51% White in both arms, reflecting the make-up of the countries where this study was conducted. See Table 5 for univariate distributions of countries, previous vaccination, and season.

Per the applicant, due to the seasonal, local, and age effects, there were some differences in bivariate distributions. For example, 49.1%, 20.9% and 30.0% of subjects 2 to <9 years of age in the full analysis population were recruited in Seasons 1, 2, and 3, respectively, while 57.0%, 19.8%, and 23.1% of the subjects in the 9 to <18-year-old age group were recruited in the respective seasons. This may have been driven by variability across country, where some countries enrolled more subjects 2 to <9 years of age (Finland, Lithuania, and Poland) and other countries (Australia and Thailand) enrolled more subjects 9 to <18 years of age. Moreover, because the focus on the 2 to <4 age group did not occur until later seasons, the percentage of Asians was higher in the 4 to <18 years of age subgroup than in the 2 to <4 years of age subgroup (50.2% vs. 36.3%, respectively). Of note, only Season 1 enrolled subjects in the Asian countries in the SH (Philippines and Thailand).

Reviewer comment: Although there were differences across some bivariate demographics, which may impact overall incidence rate estimates, because the balance across arms was maintained, the estimated VE should not be biased. Additionally, these factors (season, country, and age) were included in the proportional hazards model as random factors to control for possible differences in distributions across vaccination arms.

Table 5: Baseline Characteristics – As Randomized

	QIVc N=2258	Comparator N=2256	Total N=4514
Country (n[%])			
Australia	96 (4.3)	99 (4.4)	195 (4.3)
Estonia	599 (26.5)	599 (26.6)	1198 (26.5)
Finland	168 (7.4)	158 (7.0)	326 (7.2)
Lithuania	142 (6.3)	150 (6.6)	292 (6.5)
Philippines	902 (39.9)	898 (39.8)	1800 (39.9)
Poland	147 (6.5)	151 (6.7)	298 (6.6)
Spain	3 (0.1)	2 (0.1)	5 (0.1)
Thailand	201 (8.9)	199 (8.8)	400 (8.9)
Previous Influenza Vaccination (n[%])	1488 (65.9)	1487 (65.9)	2975 (65.9)
Season (n[%])			
Season 1 (SH)	1199 (53.1)	1196 (53.0)	2395 (53.1)
Season 2 (NH)	459 (20.3)	460 (20.4)	919 (20.4)
Season 3 (NH)	600 (26.6)	600 (26.6)	1200 (26.6)

Source: sBLA 125408/329, V130_12 CSR, p. 125-126, Table 10-6.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

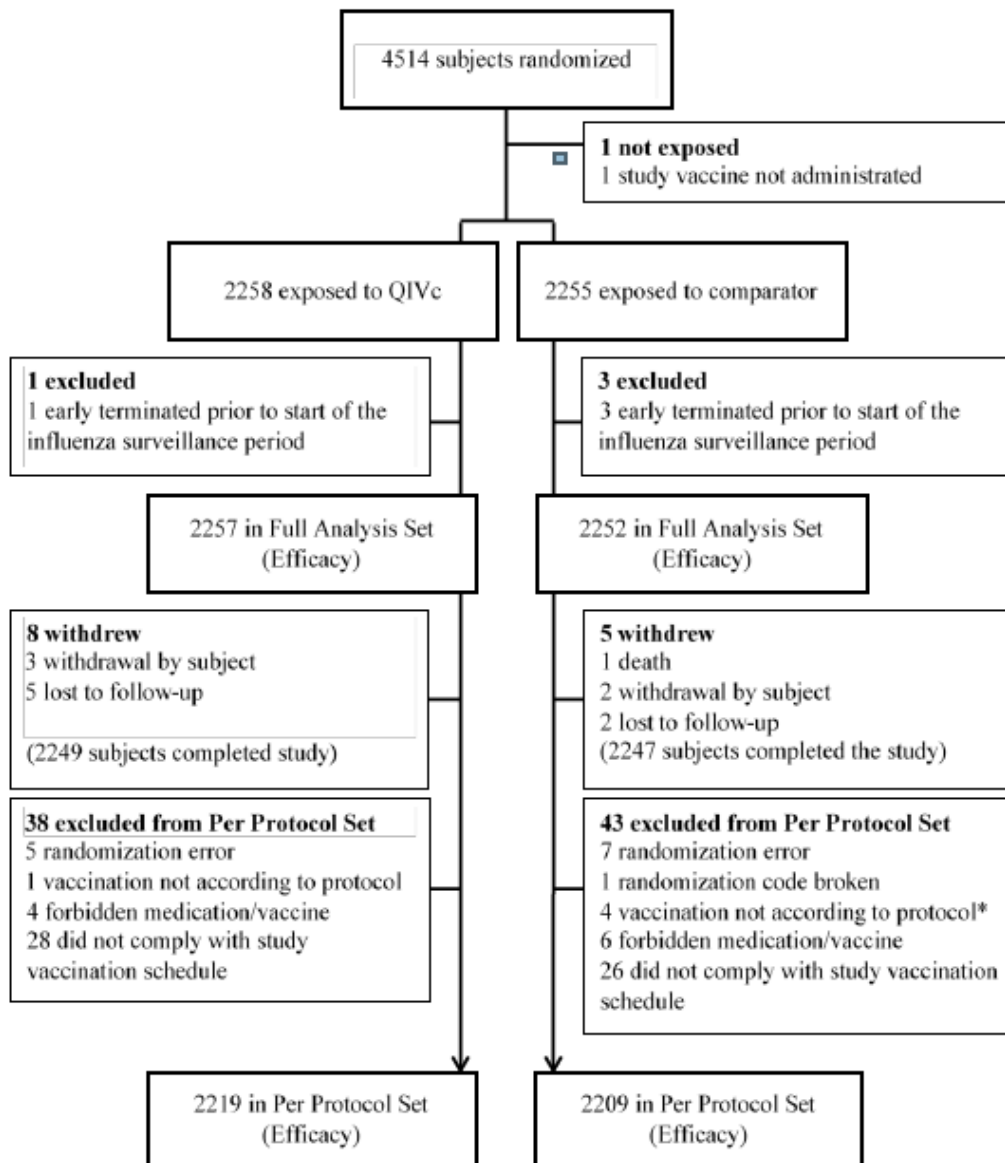
N/A

6.1.10.1.3 Subject Disposition

The study completion flowchart for the Efficacy Set is provided in Figure 1.

There were 4514 subjects randomized, with 2258 exposed to QIVc and 2255 exposed to the comparator. Withdrawals and exclusions were balanced across arms with 8 and 38 in the QIVc arm and 5 and 43 in the comparator arm, respectively. Resulting sample sizes in the per protocol set were 2219 in the QIVc arm and 2209 in the comparator arm.

Figure 1: Subject disposition for FAS and PPS (Efficacy Set)



Source: Table 14.1.1.1, Table 14.1.1.2.1, Table 14.1.1.8.1.1., Table 14.1.1.8.2.1 *There was 1 subject included twice in this category (dosage error at Visit 1, vaccine was not administrated at Visit 2). The total of the subcategories is 44. This subject was counted once in the overall total of subjects excluded from the PPS (n=43).

Source: sBLA 125408/329, V130_12 CSR, p. 108

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

In total 2444 ILIs (1193 in the QIVc group, 1251 in the comparator group) were reported in 1685 subjects (791 in the QIVc group, 894 in the comparator group). Most ILIs were reported >14 days after the last vaccination, with 1048/1193 (87.8%) in the QIVc group and 1138/1251 (91.0%) in the comparator group.

For the primary objective, in the 2 to <18 years of age group, there were 175 (7.8%) RT-PCR or culture confirmed cases in the QIVc arm and 364 (16.2%) cases in the comparator arm, for an adjusted aVE of 54.6% (95% CI: 45.7%, 62.1%). This meets the success criterion with a lower limit > 20%.

For the co-primary objective, in the 3 to <18 years of age group, there were 171 (7.7%) RT-PCR or culture confirmed cases in the QIVc arm and 351 (15.9%) cases in the comparator arm, for an adjusted aVE of 54.0% (95% CI: 44.8%, 61.7%). This meets the success criterion with a lower limit > 30%.

Reviewer comment: Of note, the confidence interval for the primary objective was also well above the CBER-defined success criterion of 95% CI lower limit above 30%.

Primary analyses of aVE were also stratified by strain. There were not enough cases due to circulating B/Victoria, so type B strains were grouped. aVE was mostly driven by the protectiveness to the A/H1N1 strain [aVE (95% CI): 80.7% (69.2%, 87.9%)]. Responsiveness to A/H3N2 and B strains were similar, with aVE (95% CI) of 42.1% (20.3%, 57.9%) and 47.6% (31.4%, 60.0%), respectively.

6.1.11.2 Analyses of Secondary Endpoints

Secondary Efficacy Endpoints: For the secondary objectives, aVE was estimated stratifying by method of confirmation (RT-PCR, culture, or culture antigenically matched) and age groups (with a focus on comparing 2 to <4 vs. 4 to <18 years of age and 2 to <9 vs. 9 to <18 years of age). The overall age groups (2 to <18 and 3 to <18 years of age) for each of the methods of confirmation are presented in Table 6.

Table 6: Number of Subjects with First-Occurrence RT-PCR-Confirmed and/or Culture Confirmed or Matched Strain Culture Confirmed Influenza and Absolute Vaccine Efficacy (95% CI), in Subjects 2 to <18 Years of Age and 3 to <18 Years of Age - FAS Efficacy

	Age: 2 to <18 QIVc n (%) N=2257	Age: 2 to <18 Comparator n (%) N=2252	Age: 2 to <18 aVE (95% CI)	Age: 3 to <18 QIVc n (%) N=2208	Age: 3 to <18 Comparator n (%) N=2201	Age: 3 to <18 aVE (95% CI)
RT-PCR or Culture Confirmed	175 (7.8)	364 (16.2)	54.6 (45.7, 62.1)	171 (7.7)	351 (15.9)	54.0 (44.8, 61.7)
RT-PCR Confirmed	175 (7.8)	364 (16.2)	54.6 (45.7, 62.1)	171 (7.7)	351 (15.9)	54.0 (44.8, 61.7)
Culture Confirmed	115 (5.1)	279 (12.4)	60.8 (51.3, 68.5)	113 (5.1)	268 (12.2)	59.9 (50.0, 67.8)
Culture Confirmed – Matched Strain	90 (4.0)	236 (10.5)	63.6 (53.6, 71.5)	89 (4.0)	225 (10.2)	62.3 (51.8, 70.5)

Source: sBLA 125408/329, V130_12 CSR, Selected results of Table 11-3, p. 133

Note: aVE is the adjusted absolute VE, as estimated by the full model.

For the 2 to <4 and 4 to <18 years of age cohorts, the secondary endpoints, RT-PCR/culture confirmed or RT-PCR alone confirmed aVE estimates (95% CI) were 62.7%

(38.1%, 77.5%) and 53.3% (43.4%, 61.5%), respectively for the two age groups. Similarly, culture-confirmed aVE estimates were 67.7% (40.8%, 82.4%) and 59.7% (49.1%, 68.1%), respectively, and culture-confirmed antigen matched aVE estimates were 77.1% (52.3%, 89.0%) and 61.6% (50.3%, 70.3%), respectively across age group.

Reviewer comment: It is notable that aVE in the 2 to <4-year-old age group was higher than the older age group. This study was extended into a third season in part to recruit more subjects in the 2 to <4-year-old age group, resulting in a change of protocol regarding this age group while the study was ongoing.

For the 2 to <9 and 9 to <18 years of age cohorts, the secondary endpoints, RT-PCR/culture confirmed or RT-PCR alone confirmed aVE estimates (95% CI) were 50.1% (38.4%, 60.2%) and 61.8% (47.4%, 72.3%), respectively for the two age groups. Culture-confirmed aVE estimates were 60.8% (49.0%, 69.8%) and 60.7% (42.1%, 73.3%), respectively, and culture-confirmed antigen matched aVE estimates were 63.0% (50.7%, 72.3%) and 64.8% (44.8%, 77.5%), respectively across age group.

Reviewer comment: There is a difference in aVE estimates in the 2 to <9-year-old age group, depending on the method of confirmation, where RT-PCR confirmed estimates were lower than the culture confirmed estimates. With RT-PCR confirmed cases, the aVE estimate was slightly lower in the younger age group, while aVE was similar across age group when based on the culture confirmed estimates.

Secondary Immunogenicity Endpoints: The immunogenicity of study vaccines was assessed 21 days after the last vaccine administration by the HI assay for the 4 viral strains included in the vaccines. Percentages of subjects achieving seroconversion and GMRs of post-vaccination to baseline GMTs are presented in Table 7. Vaccine immunogenicity appears to be higher in Season 3, compared to Season 2, which agrees with the seasonal efficacy results, where the aVE of Season 3 was higher (see Section 6.1.11.3).

Table 7: Postvaccination GMR and percentage with seroconversion of HI titers at 21 days after last vaccination in subjects 2 to <9 years of age, with 95% CIs

	Season 2 / QIVc	Season 2/ Comparator	Season 3/ QIVc	Season 3/ Comparator
N (Count)	210	212	154	145
A/H1N1 GMR	5.8 (5.1, 6.6)	1.0 (0.9, 1.1)	9.7 (7.2, 13.1)	1.2 (0.9, 1.6)
A/H1N1 SCR	59.5 (52.6, 66.2)	1.9 (0.5, 4.8)	74.0 (66.4, 80.8)	6.2 (2.9, 11.5)
A/H3N2 GMR	1.7 (1.6, 2.0)	1.0 (0.9, 1.1)	4.14 (3.5, 4.9)	1.0 (0.9, 1.2)
A/H3N2 SCR	19.0 (14.0, 25.0)	1.9 (0.5, 4.8)	51.9 (43.8, 60.0)	1.4 (0.2, 4.9)
B/Victoria GMR	3.8 (3.3, 4.3)	1.0 (0.9, 1.1)	7.01 (5.4, 9.1)	1.3 (1.0, 1.6)
B/Victoria SCR	40.0 (33.3, 47.0)	2.9 (1.1, 6.1)	58.4 (50.2, 66.3)	3.4 (1.1, 7.9)
B/Yamagata GMR	4.6 (4.0, 5.3)	1.1 (0.9, 1.3)	5.27 (4.1, 6.7)	1.1 (0.8, 1.3)
B/Yamagata SCR	49.5 (42.6, 56.5)	4.8 (2.3, 8.6)	58.4 (50.2, 66.3)	1.4 (0.2, 4.9)

Source: sBLA 125408/329, V130_12 CSR, Selected results of Table 11-10, p. 154-155

Note: In Season 2, genetic changes in the A/H3N2 strain resulting in the loss of capacity to agglutinate chicken or turkey erythrocytes. Thus, the HI assay results for this strain in season 2 are not considered reliable.

6.1.11.3 Subpopulation Analyses

- Sex: In subjects 2 to <18 years of age, aVE for the primary endpoint of QIVc compared with the comparator vaccine was similar for males (54.7% [95% CI: 42.0%, 64.6%]) and females (54.5% [95% CI: 40.6%, 65.1%]) in the FAS.
- Race: In subjects 2 to <18 years of age, the aVE for the primary endpoint of QIVc compared with comparator vaccine was similar for White subjects 54.7% [95% CI: 41.5%, 65.0%]) and for Asian subjects (53.7% [95% CI: 40.2%, 64.1%]). No other race had a large enough sample size for meaningful comparisons.
- Vaccination status: In subjects 2 to <18 years of age, the aVE for the primary endpoint of QIVc compared with comparator vaccine tended to be higher in subjects previously vaccinated against influenza (58.7% [95% CI: 47.5%, 67.5%]) as compared to those not previously vaccinated (48.4% [95% CI: 32.1%, 60.8%]).
- Season: In subjects 2 to <18 years of age, the aVEs of QIVc for the primary endpoint compared with comparator vaccine by season were: Season 1 56.6% (44.2%, 66.2%), Season 2 44.1% (20.0%, 61.1%), and Season 3 59.5% (41.0%, 72.2%).
- Country: aVE rates by country are presented in Table 8.

Table 8: Sample size and aVE estimates by country

	Australia	Philippines	Thailand	Estonia	Finland	Lithuania	Poland
N: QIVc; comparator	96; 99	902; 898	201; 199	599; 599	168; 158	142; 150	147; 151
aVE (95%CI)	93.7 (52.3, 99.2)	56.7 (43.0, 67.1)	23.9 (-53.1, 62.1)	46.9 (23.2, 63.2)	38.3 (-2.8, 63.0)	58.8 (21.2, 78.4)	88.0 (60.3, 96.4)

Source: sBLA 125408/329, V130_12 CSR, Selected results of Table 11-9, p. 151

Note: Sample size in Spain was too small for a country-specific aVE estimate.

Reviewer comment: The study was extended partly in response to an over-enrollment in the Philippines in season 1. Though there are large confidence intervals in the case of some countries, the aVE estimate for the Philippines is not out of line with the other countries.

6.1.11.4 Dropouts and/or Discontinuations

Less than 0.5% of subjects were lost to follow-up or withdrew prior to completing the study. Dropouts were balanced by arm.

Reviewer comment: With a low and balanced dropout rate, aVE estimates are unlikely to be substantially biased.

6.1.11.5 Exploratory and Post Hoc Analyses

N/A

6.1.12 Safety Analyses

Of the 4514 subjects who were enrolled and randomized into the study, 4513 subjects were exposed to the study vaccines and were included in the overall Safety and Unsolicited Safety Sets. Four (0.1%) of the enrolled subjects (3 QIVc, 1 comparator) did not return the adverse event diary and were excluded from the Solicited Safety Set (n=4509). Approximately one-third of the enrolled subjects (34%) received a 2-dose study vaccination (n=1524).

Overall, adverse event rates were similar across vaccination arm. This held consistently across subgroup analyses.

Solicited Adverse Events

The rates of solicited AEs reported within 30 minutes after any vaccination were 9.5% and 7.3% in the QIVc and comparator groups, respectively, and of these, most were local adverse events. For any solicited AE reported from Day 1 (6 hours) through Day 7 after vaccination, the rates were 51.4% in the QIVc group and 48.6% in the comparator group. Of these, the rates of local and systemic solicited AEs were similar across arm (local/systemic: 36.8%/31.4% for QIVc and 33.6%/30.5% for the comparator). Except for a slightly higher rate of pain/tenderness in the QIVc group (23.8%/28.7%) versus the comparator (19.0%/25.4%), there were no notable differences in rates of specific solicited local AEs across vaccine arms. Duration of solicited local AEs was approximately 4-5 days and was comparable across the two arms.

Reviewer comment: The above solicited AEs were reported for after any vaccination. Since the second vaccination in the comparator arm was a placebo, higher rates of solicited AEs in the QIVc arm are likely a reflection of the comparison of the second vaccination versus the placebo. The solicited AE rates in this study were lower than those reported in Study V130_03 (QIVc arm, Day 1 through 7: 72% any solicited AE, 66% local solicited AE), which was the pediatric study (ages 4 to <18 years of age) submitted for the accelerated approval of QIVc.

Subgroup Analyses: Solicited local AEs

- Age group (2 to <6, 6 to <9, and 9 to <18 years of age) and first/second/any vaccination: After the first vaccination, AEs were similar across age group and study arm, for both the first 30 minutes after vaccination and Day 1 – Day 7. Comparing the second vaccination to the first, AE rates were similar in the 2 to <6 age range, but generally lower in the 6 to <9 years of age (e.g. any AE Day 1 – Day 7 rate was 46.8% after Dose 1 vs. 37.6% after Dose 2).
- No notable differences in frequencies of subjects 2 to <18 years of age who reported solicited local AEs were observed in the subgroup analysis by sex.
- The proportion of subjects 2 to <18 years of age reporting any solicited local AEs 6 hours on Day 1 through 7 days after the first vaccination was higher in White subjects (47.1% [QIVc], 46.1% [comparator]) than in Asian subjects (19.4%

[QIVc], 17.0% [comparator]) in both vaccine groups. A similar difference in AE rates across race was observed at 30 minutes postvaccination.

- The proportion of subjects with solicited local AEs after any vaccination was lower in previously vaccinated subjects compared to those not previously vaccinated for each local AE.

Subgroup Analyses: Solicited systemic AEs

Subgroups analyses of solicited systemic AEs showed the same patterns as in the solicited local AEs.

- Age group (2 to <6, 6 to <9, and 9 to <18 years of age) and first/second/any vaccination: There were few systemic AEs reported in the 30 minutes after vaccination, and thus no differences were observed between vaccine arms across all age groups. There appear to be occasional small numerical differences across study arm in some specific examples, such as pain at injection site for subjects 6 to <9 years of age (QIVc: 8.0% vs. comparator: 4.9%) and 9 to <18 years (QIVc: 4.7% vs. comparator: 3.8%). However, due to the large number of subgroups, that these examples may be due to sampling variability. There were no notable differences to signal a specific adverse event, and in fact, most solicited systemic adverse event rates were < 1%.
- No notable differences in frequencies of subjects 2 to <18 years of age who reported solicited systemic AEs were observed in the subgroup analysis by sex.
- The proportion of subjects 2 to <18 years of age reporting any solicited systemic AEs from 6 hours on Day 1 through 7 days after any vaccination was higher in White subjects (37.7% [QIVc], 35.9% [comparator]) than in Asian subjects (24.5% [QIVc], 24.7% [comparator]) in both vaccine groups. No difference in AE rate was found at 30 minutes postvaccination.
- The proportion of subjects with solicited systemic AEs after any vaccination was lower in previously vaccinated subjects compared to those not previously vaccinated.

Unsolicited Treatment Emergent Non-Serious Adverse Events

Proportions of subjects reporting at least one unsolicited AE after any vaccination were similar across arms (28.0% and 27.9% in the QIVc and comparator groups, respectively), and most were mild or moderate. Of these, 4.3% and 3.9% were considered vaccine related (QIVc and comparator, respectively).

6.1.12.1 Methods

For definitions and method of collection of adverse events, please refer to the clinical review. Results were presented descriptively as percentages and 95% CIs.

6.1.12.3 Deaths

During the study, there was 1 death (<0.1%) in the comparator group, which occurred during the follow-up period and was not attributed to the study treatment.

6.1.12.4 Nonfatal Serious Adverse Events

The proportion of unsolicited serious adverse events was 1.1% and 1.3% in the QIVc and comparator arms, respectively, though none were considered vaccine related.

Reviewer comment: The SAE rate for the QIVc arm in this study is higher than that reported in Study V130_03 (0.5%). However, these rates are too low to conclude if there is a meaningful difference when compared to the current study.

6.1.12.5 Adverse Events of Special Interest (AESI)

Please see the clinical review.

6.1.12.6 Clinical Test Results

Please see the clinical review.

6.1.12.7 Dropouts and/or Discontinuations

None of the subjects withdrew from the study prematurely due to an AE with onset from Day 1 through end of the study.

7. INTEGRATED OVERVIEW OF EFFICACY

N/A

8. INTEGRATED OVERVIEW OF SAFETY

N/A

9. ADDITIONAL STATISTICAL ISSUES

N/A

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Vaccine efficacy was adequately demonstrated in this study, with an estimate (95% CI) of 54.6% (95% CI: 45.7%, 62.1%) in the 2 to <18 years of age group. Acceptable aVE was also demonstrated in possible prognostic subgroups (age, season, and country). In particular, in Season 2, there may have been less of a genetic match than the other two seasons, and the vaccine still showed reasonable efficacy, with an aVE of 44.1% (20.0%, 61.1%).

During the study, the decision was made to extend into a third season. The stated reasoning can be considered as externally driven (over-enrollment in the Philippines in Season 1, counter-act the under-enrollment in the 2 to <4 years of age group). Since the

aVE appears to be consistent across age and country, this extension does not appear to negatively impact the study results.

The safety analyses showed that AE rates were similar when QIVc was compared to the MenACWY vaccine, and only slightly higher when compared to the placebo for the second dose. Reported AEs were generally local, low grade, and with limited duration. There were some differences across race, but this may be due to differences across country or other confounders.

10.2 Conclusions and Recommendations

Efficacy and safety results support full approval of the QIVc, Quadrivalent Flucelvax, in the 2 to <18-year-old age range.