Application Type	Supplementary Biologics Licensing Application (sBLA)
STN	125408/351
CBER Received Date	December 14, 2020
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Division / Office	OVRR
Committee Chair	Josephine Resnick, Ph.D.
Clinical Reviewer(s)	Jonathan Albert, M.D.
Project Manager	Paul Keller, Ph.D.; Joseph Kulinski, Ph.D.
Priority Review	No
Reviewer Name(s)	Elizabeth Teeple, Ph.D.
Review Completion Date / Stamped Date	
Concurrence	Lei Huang, Ph.D. Concurring Reviewer, Viral and Bioassay Team, VEB, DB, OBE
	Tsai-Lien Lin, Ph.D. Chief, Vaccine Evaluation Branch, DB, OBE
Applicant	Seqirus, Inc.
Established Name	Quadrivalent inactivated vaccine, cell-derived (QIVc)
(Proposed) Trade Name	Flucelvax
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants	Influenza vaccine strains (Northern Hemisphere 2019/2020): 15 µg per strain A/Idaho/07/2018 (A/H1N1) A/Indiana/08/2018 (A/H3N2) B/Singapore/INFTT-16-0610/2016 (B/Yamagata) B/Iowa/06/2017 (B/Victoria)
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 6 months 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 6 months 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
B/Yam, B/Vic	B/Yamagata and B/Victoria strains of the influenza vaccine
BIMO	Bioresearch Monitoring
BLA	Biologic Licensing Application
CBER	Center for Biologics Evaluation, Research and Review
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CMI	Cell-Mediated Immunity
CSR	Clinical Study Report
FAS	Full Analysis Set
FDA	Food and Drug Administration
GMT/R	Geometric Mean Titer/Ratio
HAI	Hemagglutination Inhibition
IM	Intramuscular
LLOQ	Lower Limit of Quantitation
MDCK	Madin-Darby Canine Kidney
MN	Microneutralization
NH	Northern Hemisphere
NI	Non-inferiority
NOCD	New Onset of Chronic Disease
PI	Prescribing Information
PPS	Per-Protocol Set
QIV	Quadrivalent Egg-based Influenza Virus Vaccine
QIVc	Quadrivalent Cell-based Influenza Virus Vaccine
SAE	Serious Adverse Event
SCR	Seroconversion Rate
sBLA	Supplemental Biologic Licensing Application
TIVc	Trivalent Cell-based Influenza Virus Vaccine
UL	Upper Limit
VE	Vaccine Efficacy

1. EXECUTIVE SUMMARY

The applicant, Seqirus, submitted this supplemental Biologics Licensing Application (sBLA) in support of an extension of the pediatric indication of Flucelvax quadrivalent, a quadrivalent cell-based influenza vaccine (QIVc), to include the 6 to <24 months of age group. This submission contains the results of Study V130_10, a Phase 3, stratified, randomized, observer blind, multicenter study to evaluate safety and immunogenicity of the QIVc compared to a licensed egg-based quadrivalent influenza vaccine (QIV), Afluria, in subjects 6 to <48 months of age. The population under study in V130_10 includes a two-year overlap with the previous efficacy trial, V130_12. Thus, while success is evaluated in the full age range of study V130_10, the age range 6 to <24 months is also evaluated in this review.

Overall, V130_10 demonstrated non-inferiority (NI) of immunogenicity for QIVc compared to QIV in the four strains, A/H1N1, A/H3N2, B/Yamagata (B/Yam), and B/Victoria (B/Vic), as measured by a ratio of Geometric Mean Titers (GMT/GMR) and a difference of seroconversion rates (SCR). For A/H1N1 and the B strains, results were based on the standardly used hemagglutination inhibition (HAI) assay. However, in the previous season, the hemagglutination inhibition (HAI) assay did not agglutinate for the A/H3N2, so pre-specified success criteria for the A/H3N2 strain were based on the microneutralization (MN) assay. Key findings with respect to immunogenicity are summarized below:

- GMRs (95% confidence intervals [CIs]) for the four strains (Afluria to Flucelvax QIVc) were: 0.73 (0.65, 0.84), 1.04 (0.93, 1.16), 0.73 (0.66, 0.81), and 0.88 (0.79, 0.97) for the A/H1N1, A/H3N2, B/Yam, and B/Vic strains, respectively. These all met the NI success criteria of upper limit (UL) of the 95% CI < 1.5.
- Differences of SCRs (95% CIs) for the four strains (Afluria minus Flucelvax QIVc) were: -11.5% (-16.4%, -6.4%), 3.1% (-1.4%, 7.8%), -14.9% (-19.6%, -10.0%), and -6.0% (-10.3%, -1.4%) for the A/H1N1, A/H3N2, B/Yam, and B/Vic strains, respectively. These all met the NI success criteria of 95% CI UL < 10%.
- Primary analyses were based on assays using cell-derived target strains. Egg-derived strains are likely to introduce more mutations to the target strains. Alternatively, cell-derived target strains are expected to introduce fewer mutations and better match the QIVc. Thus, it is of note that non-inferiority criteria were also met using egg-derived target strains.
- The data set used for analyses, the Per Protocol Set (PPS), excluded 29% of the full data set in the QIVc arm and 26% in the QIV arm. As this was higher than planned in the protocol, further analyses were requested and confirmed these exclusions did not alter the study conclusions.

The safety profile of QIVc is similar to QIV. There are no major safety concerns from the statistical perspective.

Overall, efficacy and safety results support approval of an extension of the pediatric indication of Flucelvax Quadrivalent to 6 to <24-month-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 20 November 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 17 September 2015.

The applicant then submitted a major amendment seeking traditional approval of a quadrivalent version of Flucelvax (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 23 May 2016, and the approval was extended to TIVc in age 4 years and above at the same time.

The pediatric study for children 6 months to <4 years of age was deferred as Study V130_10 was ongoing. In the interim, the QIVc confirmatory study, V130_12, was submitted to the BLA, and QIVc was approved for use in persons 2 years of age and older under traditional approval in March 2021.

This supplemental BLA is submitted in fulfillment of the remaining postmarketing requirement under PREA, which is to evaluate the safety and immunogenicity of Flucelvax in pediatric subjects 6 months to <2 years of age.

2.1 Disease or Health-Related Condition(s) Studied

Influenza in children from 6 months to <4 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 U.S. since May 2016 and in individuals aged 9 years and older in Europe since December 2018, Canada since November 2019, and Australia since August 2020. QIVc was approved in Brazil for use in adults 18 years and older on 26 February 2020 and in children 2 years and older on 09 June 2020 and in Taiwan for use in adults and children 3 years and older on 23 March 2020.

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 acceptable for conducting a complete statistical review.

3.2 Compliance With Good Clinical Practices And Data Integrity

Please see the Bioresearch Monitoring (BIMO) review for a 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_10.

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

The main study was submitted in STN 125408/351.0, 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 5.2, Tabular Listing of All Clinical Studies
- Module 5.3.5.1. Study V130_10 Clinical Study Report

Additional analyses on missing data were conducted, with results submitted to STN 125408/351.4. This amendment is also considered in this review.

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_10/ 2019/2020	US	Safety; Immunogenicity	Phase 3 Observer-blind, randomized, controlled (influenza vaccine comparator)	QIVc Afluria® Quadrivalent 1 or 2 vaccinations of 0.5 mL (QIVc) or 0.25/0.5 mL (Afluria Quadrivalent*), 4 weeks apart, IM	Total 2414 1605 in the QIVc group and 809 in the control group	Healthy children aged 6 to <48 months

Abbreviations: IM = intramuscular; QIVc = Cell culture-derived quadrivalent influenza vaccine.
Source: Derived from STN 125408/351/0, 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_10

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

6.1.1 Objectives

Primary Immunogenicity Objective

To demonstrate that vaccination with QIVc elicits an immune response that is not inferior to that of a US-licensed QIV containing the recommended strains for the season, in subjects 6 months through 47 months of age, as measured by HAI assay for A/H1N1, B/Yamagata, and B/Victoria strains and by MN assay for A/H3N2 strain, using cell-derived target viruses.

Secondary Immunogenicity Objectives

1. To describe the immunogenicity of QIVc and US-licensed QIV by HAI assay for A/H1N1, B/Yamagata, and B/Victoria strains, and by MN assay for A/H3N2 strain, using egg-derived target viruses.
2. To describe the immunogenicity of QIVc and US-licensed QIV by HAI assay for A/H1N1, B/Yamagata, and B/Victoria strains, and by MN assay for A/H3N2 strain, using cell-derived target viruses.
3. To describe the immunogenicity of QIVc and US-licensed QIV by MN assay for A/H1N1, B/Yamagata, and B/Victoria strains, in a subset of subjects, using cell-derived targets.

Secondary Safety Objective

The secondary safety objective was to evaluate the safety and reactogenicity of QIVc and US-licensed QIV.

Reviewer comment: During the study planning, the H3N2 strain had mutated and was unable to agglutinate in the hemagglutination inhibition (HAI) assay. CBER requested a comparability study and agreed to base the primary endpoints for the H3N2 strain on the microneutralization (MN) assay. However, in the year this study was conducted, the H3N2 strain had mutated, and the issues with agglutination were no longer an issue. The HAI assay was conducted as an exploratory endpoint and was measured on all participants. Thus, while the MN assay endpoint is still the pre-specified primary endpoint, the HAI assay endpoint may be more relevant and comparable to other vaccine

immunogenicity measures. The HAI endpoints for the H3N2 strain was also considered in support of the pre-specified endpoints.

6.1.2 Design Overview

This study was designed as a Phase 3, randomized, observer-blind, multicenter noninferiority study to evaluate safety and immunogenicity of QIVc compared to a US-licensed QIV in healthy male and female children 6 months to < 48 months of age. Infants and toddlers were randomized to receive QIVc or QIV in a 2:1 ratio and stratified so that at least 30% of participants would be 6 to 23 months of age and at least 30% of participants would be 24 to 47 months of age. Previously vaccinated participants received 1 dose, and not previously vaccinated participants received 2 doses. For the Immunogenicity Group (planned to include approximately 2418 participants), influenza Type A and B specific antibodies were measured. A smaller Cell-Mediated Immunity (CMI) population (planned to include approximately 84 subjects) were enrolled to measure CMI responses descriptively, with any remaining sera used for immunogenicity bridging with the larger group. Study V130_10 was conducted during the Northern Hemisphere 2019/2020 influenza season.

6.1.3 Population

Healthy subjects aged 6 to <48 months of age.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Investigational Vaccine: QIVc

QIVc is a cell-based quadrivalent inactivated subunit seasonal influenza vaccine manufactured by Seqirus. Participants in the QIVc group received one or two 0.5 mL IM doses of QIVc (depending on influenza vaccination history). An approximately 0.5 mL dose of QIVc contains nominally 15 μg of hemagglutinin (HA) of each of the four influenza strains (60 μg total). The strain composition of QIVc used in this study was:

- A/Idaho/07/2018 (A/H1N1).
- A/Indiana/08/2018 (A/H3N2).
- B/Singapore/INFTT-16-0610/2016 (B/Yamagata).
- B/Iowa/06/2017 (B/Victoria).

The product lot number was 261303 (expiry date: 19 June 2020).

US-licensed QIV comparator vaccine: Afluria Quadrivalent inactivated influenza virus vaccine

The US-licensed QIV comparator vaccine, Afluria Quadrivalent, is an inactivated quadrivalent influenza vaccine manufactured by Seqirus. Participants in the QIV group received one or two 0.25mL or 0.5 mL IM doses of QIVc (depending on influenza vaccination history and age group <36 months). An approximately 0.25mL (0.5 mL) dose of QIVc contains nominally 7.5 (15) μg of HA of each of the four influenza strains (30 or 60 μg total). The strain composition of QIV used in this study was:

- A/Brisbane/02/2018 (IVR-190) (A/H1N1).

- A/Kansas/14/2017 (X-327) (A/H3N2).
- B/Phuket/3073/2013 (BVR-1B) (B/Yamagata).
- B/Maryland/15/2016 (B/Victoria).

The product lot numbers of Afluria Quadrivalent used in the study were P100100543 (expiry date: 16 May 2020) for the 0.5 mL dose and P100118460 (expiry date: 30 June 2020) and P100114135 (expiry date: 30 June 2020) for the 0.25 mL dose.

Reviewer comment: Per the CDC, the recommended components for the 2019-2020 seasonal influenza vaccine were:

- *A/Brisbane/02/2018 (H1N1)pdm09-like virus (updated)*
- *A/Kansas/14/2017 (H3N2)-like virus (updated)*
- *B/Phuket/3073/2013-like (Yamagata lineage) virus*
- *B/Colorado/06/2017-like (Victoria lineage) virus*

(source: https://www.cdc.gov/flu/season/faq-flu-season-2019-2020.htm, retrieved on 09 April 2021). As this is an immunogenicity study, it is not clear how difference in strain components will impact effectiveness on reducing influenza diseases. Additionally, the primary analysis is based on cell-derived strains that matched the components in the study vaccine. Secondary analyses based on the egg-derived strains that are included in the comparator vaccine are supportive. I defer to the clinical reviewer on the overall interpretation of the impact of the difference in strains.

6.1.6 Sites and Centers

This study was conducted at 47 centers in the U.S.

6.1.7 Surveillance/Monitoring

Please refer to the clinical review and the BIMO review.

6.1.8 Endpoints and Criteria for Study Success

Co-Primary Immunogenicity Endpoints

- Serum HAI antibody titer against A/H1N1, B/Yamagata, and B/Victoria vaccine strains at Day 29/57, using cell-derived target viruses:
  o GMT by HAI assay
  o SCR defined as the percentage of subjects with either a pre-vaccination HAI titer <1:10 and a post-vaccination HAI titer ≥1:40, or a pre-vaccination HAI titer ≥1:10 and a ≥4-fold increase in post-vaccination HAI titer
- Serum neutralizing antibody titer against A/H3N2 vaccine strain at Day 29/57, using cell-derived target viruses:
  o GMT by MN assay
  o SCR defined as the percentage of subjects with either a pre-vaccination MN titer <1:10 and a post-vaccination MN titer ≥1:40, or a pre-vaccination MN titer ≥1:10 and a ≥4-fold increase in post-vaccination MN titer

With four strains and 2 endpoints, there are a total of 8 co-primary endpoints.

Secondary Immunogenicity Endpoints

- Humoral immune response in terms of HAI antibodies against A/H1N1, B/Yamagata, and B/Victoria strains, using cell- and egg-derived target viruses:
  - GMT by HAI assay at Days 1 and 29/57
  - Geometric mean ratio (GMR), defined as the fold increase in serum HAI GMT post-vaccination (Day 29/57) compared to pre-vaccination (Day 1)
  - Seropositivity rates (percentages of subjects with HAI titer ≥1:10) at Days 1 and 29/57
  - Percentages of subjects with HAI titer ≥1:40 at Days 1 and 29/57
  - SCR by HAI assay
- Neutralizing antibody titers against A/H3N2 vaccine strains, using cell- and egg-derived target viruses:
  - GMT by MN assay at Days 1 and 29/57
  - GMR, defined as the fold increase in serum MN GMT post-vaccination (Day 29/57) compared to pre-vaccination (Day 1)
  - Seropositivity rates (percentages of subjects with MN titer ≥1:10 [lower limit of quantification (LLOQ)]) at Days 1 and 29/57
  - SCR by MN assay
- Neutralizing antibody titers against A/H1N1, B/Yamagata, and B/Victoria vaccine strains, in a subset of subjects:
  - GMT by MN assay at Days 1 and 29/57
  - GMR, defined as the fold increase in serum MN GMT post-vaccination (Day 29/57) compared to pre-vaccination (Day 1)
  - Seropositivity rates (percentages of subjects with MN titer ≥1:10 [LLOQ]) at Days 1 and 29/57
  - SCR by MN assay

Secondary Safety Endpoints

- Solicited adverse events (AEs) within 7 days after each study vaccination
- Any unsolicited AEs from Day 1 to Day 29 (in previously vaccinated subjects) and from Day 1 to Day 57 (in not previously vaccinated subjects)
- Percentage of subjects with any SAEs, New Onset of Chronic Disease (NOCD), or AEs leading to withdrawal during the entire study period (i.e., from Day 1 to Day 181 for previously vaccinated subjects or from Day 1 to Day 209 for not previously vaccinated subjects)

6.1.9 Statistical Considerations & Statistical Analysis Plan

Infants and toddlers were enrolled and randomized to receive QIVc or Afluria in a 2:1 ratio, with stratification by age to ensure at least 30% of subjects in the 6 to < 24 months of age range and at least 30% of subjects in the 24 to < 36 months of age range. The protocol planned for a sample size of 2418 healthy male and female children at 6 to <48 months of age for evaluation of immunogenicity, with another 84 children age 24 to <48 months of age for an exploratory evaluation of CMI.

Study vaccines were administered in observer-blind fashion. Unblinded personnel

administered the vaccine. After vaccination, safety assessments and study related procedures were performed by blinded team members.
The following analysis populations were considered:

- Full Analysis Set (FAS): all enrolled children who received at least one dose of the study vaccine. In case of vaccination error, subjects in the FAS were analyzed "as randomized". The FAS was used for descriptive baseline characteristic analyses.
- Overall Safety Set: all children in the FAS who were assessed for relevant safety data (e.g. solicited or unsolicited AE data). The safety set population was analyzed "as treated."
- FAS Immunogenicity: all children in the FAS who received the Day 1 vaccine and provided valid serology specimens from Day 1 and Day 29/57, as specified in the protocol. In case of vaccination error, subjects in the FAS Immunogenicity were analyzed "as randomized".
- Per Protocol Set (PPS): all children in the FAS Immunogenicity set who correctly received the vaccine and had no major protocol deviations medically assessed as having potential to impact the immunogenicity results (e.g. vaccination or blood draw out of schedule, concomitant infection which may influence vaccine-specific immune responses, serological results not available).

The PPS was used for the primary and secondary immunogenicity analyses, with supporting analyses performed using the FAS Immunogenicity.

For immunogenicity analyses, subgroup analyses included:

- Subjects with a pre-vaccination HAI titer <1:10 and pre-vaccination HAI titer ≥1:10
- Subjects with a pre-vaccination MN titer <1:10 and pre-vaccination MN titer ≥1:10
- Subjects with and without recent seasonal influenza vaccine (defined as influenza vaccine within the past 12 months)
- Subjects "previously vaccinated" and "not previously vaccinated"
- Subjects aged "6 through 23 months" and "24 through 47 months"
- Subjects by center
- Subjects by gender
- Subjects by race
- Subjects by ethnicity

For safety analyses, subgroup analyses included:

- Subjects "previously vaccinated" and "not previously vaccinated"
- Subjects with and without recent seasonal influenza vaccine (defined as influenza vaccine within the past 12 months)
- Subjects aged "6 through 23 months" and "24 through 47 months"
- Subjects by gender
- Subjects by race
- Subjects by time interval as below:

- Day 1 to Day 29, Day 29 to Day 181 in "previously vaccinated" subjects
- Day 1 to Day 57, Day 57 to Day 209 in "not previously vaccinated" subjects

This study was designed to demonstrate the non-inferiority (NI) of the study vaccine QIVc to the licensed vaccine, Afluria. Analyses are based on 8 co-primary post-vaccination GMT and seroconversion endpoints, where seroconversion is defined as follows:

- A pre-vaccination titer <1:10 and a post-vaccination titer ≥1:40, or
- A pre-vaccination titer ≥1:10 and a ≥4-fold increase in post-vaccination titer.

Reviewer comment: The definition of seroconversion applies to both the HAI and MN assay titers.

NI was assessed with the following hypothesis tests. Let $i = 1, \ldots, 4$ index the four strains (A/H1N1, A/H3N2, B/Yamagata, and B/Victoria).

- H_0: $Ri > 1.5$ for any strain vs. H_A: $Ri \leq 1.5$ for all four strains and
- H_0: $Di > 10$ for any strain vs. H_A: $Di \leq 10$ for all four strains.

Here, *Ri* is the post-vaccination GMT ratios of Afluria /QIVc for strain *i* and *Di* percent difference in the seroconversion rates (SCR) of $SCR_{Afluria}$ - SCR_{QIVc}, for strain *i*.

Immunogenicity was assessed by HAI and MN assays at Days 1 and 29/57. Continuous measure analyses were performed on the log 10 titer values. Individual titers below the LLOQ (<10) were set to half of that limit (5). For each of the four strains, the SCRs were presented with point estimates and exact 95% Clopper-Pearson CIs and differences in SCRs were presented with point estimates and 95% Miettinen-Nurminen CIs. For each of the four strains, the GMT ratio (GMR) was estimated using the general linear model (GLM):

Log-10 postvaccination titer = Vaccine + Age Strata + Gender + Vaccination History [y/n] + Log-transformed prevaccination titer + Site + Age Strata*Vaccine.

Model-based least square means (on the log scale) estimates and 95% CIs were used to assess the hypothesis tests. If all 8 co-primary endpoints demonstrated noninferiority, then overall noninferiority of QIVc compared with the US-licensed comparator QIV was concluded. Thus, no adjustment for multiplicity was needed.

Immunogenicity analyses were based on complete case only, assuming missing completely at random for unbiased estimates. Imputation methods were not used.

The study was designed to achieve at least 90% power, using a 1-sided alpha = 0.025. GMR and SCR assumptions were based on a previous Phase 1/2 dose-finding study in 6 to <48-month-old children (V58P16) as follows:

- GMRs for QIVc = 1.49 for the A/H1N1 strain, 1.00 for the A/H3N2 strain (based on the MN assay), and 0.84 for the two B strains. Standard deviation of log (titer) was assumed to be 1.3 across all strains.

- The SCRs for the A/H1N1, B strains, and A/H3N2 were assumed to be 81%, 69%, and 85%, respectively. The expected difference between SCRs was assumed to be 7% for A/H1N1, 5% for A/H3N2 (based on the MN assay), and 0% for the Type B strains.

With n=1450 QIVc and n=725 QIV evaluable participants, overall power was estimated as 94% under the above assumptions. With assumed 10% dropout, n=2418 would be recruited for the study. With the additional n=84 toddlers (24 through <48 months of age) in the exploratory CMI Population, the total sample size was expected to be 2502 participants.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Please see Table 2 for the Immunogenicity Analysis Set counts.

Table 2: Overview of Immunogenicity Sets Analyzed – As Randomized

	QIVc n (%)	**US-licensed QIV n (%)**	**Total n (%)**
All Enrolled Set	1605	809	2414
All Exposed Set (FAS) [a]	1597 (99.5)	805 (99.5)	2402 (99.5)
FAS excluding the CMI Population	1547	775	2322
FAS Immunogenicity[b]	1169 (75.6)	618 (79.7)	1787 (77.0)
PPS[b]	1092 (70.6)	575 (74.2)	1667 (71.8)

[a] The All Exposed Set includes the Immunogenicity and CMI subsets. The applicant also refers to this group as the Full Analysis Set (FAS)
[b] The FAS Immunogenicity and the PPS exclude the CMI Population. The denominator for the percentages for these sets is the FAS excluding the CMI Population.
Note 1: Subjects could be excluded from the FAS Immunogenicity and PPS for more than 1 reason.
Source: Original sBLA 125408/351; CSR V130_10, Table 10-3, pp. 84.

Primary and secondary immunogenicity analyses were replicated using the FAS Immunogenicity set because there was >5% difference in the total number of subjects between the PPS (N=1667) and FAS Immunogenicity (N=1787). The most common reason for exclusion from the FAS Immunogenicity was missing serological results (15.9%); the most common reasons for exclusion from the PPS were not complying with the study vaccination schedule (4.0%) and not complying with the blood draw schedule (3.4%).

The applicant also reported that 86.2% of participants completed the protocol, with the primary reason for discontinuation being loss to follow-up (11%, with 11.9% in the QIVc arm and 9.4% in the Afluria arm).

Reviewer comment: It is not clear why there is a slight difference in exclusion rates (e.g. excluded from FAS Immunogenicity or PPS) across treatment arms. The potential impact of this difference on the immunogenicity analyses is discussed further in Section 6.1.11.4.

6.1.10.1.1 Demographics

Demographics were generally well-balanced across study arms (Table 3). The applicant met the goal of at least 30% enrolled in both age groups, with 37% in the 6 to <24 months age group and 63% in the 24 to <48 months age group.

Overall, the study population was balanced with respect to sex. Most subjects were White or Black/African American and predominantly not of Hispanic or Latino origin. Previous vaccination status was evenly distributed across group (52% with previous vaccination, 48% without). However, the proportion of previously vaccinated subjects increased as the number of exclusions increased. Specifically, 50.7% of the FAS were previously vaccinated, whereas 57.0% of the FAS Immunogenicity population and 59.8% of the PPS population were previously vaccinated.

Table 3: Demographics and Baseline Characteristics (Full Analysis Set)

	QIVc (N=1597)	**US-licensed QIV (N=805)**	**Total (N=2402)**
Age (months): Mean (SD)	28.1 (11.5)	28.2 (11.6)	28.1 (11.6)
Age group (n[%])			
6 months to 23 months	595 (37.3)	299 (37.1)	894 (37.2)
24 months to 47 months	1002 (62.7)	506 (62.9)	1508 (62.8)
Sex (n[%])			
Male	803 (50.3)	406 (50.4)	1209 (50.3)
Female	794 (49.7)	399 (49.6)	1193 (49.7)
Race (n[%])			
White	1039 (65.1)	539 (67.0)	1578 (65.7)
Black or African American	455 (28.5)	209 (26.0)	664 (27.6)
Asian	13 (0.8)	8 (1.0)	21 (0.9)
Native Hawaiian or Other Pacific Islander	8 (0.5)	6 (0.7)	14 (0.6)
American Indian or Alaska Native	11 (0.7)	11 (1.4)	22 (0.9)
Other	71 (4.4)	32 (4.0)	103 (4.3)
Ethnic origin* (n[%])			
Hispanic or Latino	434 (27.2)	226 (28.1)	660 (27.5)
Not Hispanic or Latino	1160 (72.6)	575 (71.4)	1735 (72.2)
Previously vaccinated (n[%])	810 (50.7)	430 (53.4)	1240 (51.6)
Body mass index (kg/m2): Mean (SD)	17.0 (2.5)	17.25 (3.0)	17.1(2.7)

**This category does not sum to 100%. Remaining participants are unknown or not reported.*
Source: Adapted from - sBLA 125408/351; CSRV130_10, pp. 88-89.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

N/A

6.1.10.1.3 Subject Disposition

Subject disposition is reported in Table 4.

Table 4: Overview of Immunogenicity Analysis Sets, Including Reasons for Exclusion

	QIVc n (%)	US-licensed QIV n (%)	Total n (%)
All Enrolled Set[a]	**1605**	**809**	**2414**
Study vaccine not administered at all	8 (0.5)	4 (0.5)	12 (0.5)
FAS[a]	**1597 (99.5)**	**805 (99.5)**	**2402 (99.5)**
FAS excluding the CMI Population	**1547**	**775**	**2322**
Early terminated prior to V2 (previously vaccinated) or V3 (not previously vaccinated)	135 (8.7)	56 (7.2)	191 (8.2)
Serological results not available	260 (16.8)	109 (14.1)	369 (15.9)
FAS Immunogenicity[b]	**1169 (75.6)**	**618 (79.7)**	**1787 (77.0)**
Concomitant infection which may influence vaccine-specific immune responses	9 (0.6)	2 (0.3)	11 (0.5)
Did not comply with blood draw schedule	48 (3.1)	30 (3.9)	78 (3.4)
Did not comply with study vaccination schedule	65 (4.2)	29 (3.7)	94 (4.0)
Forbidden vaccination or non-study vaccination	10 (0.6)	6 (0.8)	16 (0.7)
Randomization code was broken	0	1 (0.1)	1 (<0.1)
Subject did not meet entry criteria	2 (0.1)	4 (0.5)	6 (0.3)
Vaccination not according to protocol	40 (2.6)	14 (1.8)	54 (2.3)
PPS[b]	**1092 (70.6)**	**575 (74.2)**	**1667 (71.8)**

[a] The All Enrolled Set and the FAS include the CMI Population. The denominator for the percentages presented for the FAS is the All Enrolled Set.
[b] The FAS Immunogenicity and the PPS exclude the CMI Population. The denominator for the percentages presented for these sets is the FAS excluding the CMI Population.
Note 1: Subjects could be excluded from the FAS Immunogenicity and PPS for more than 1 reason.
Source: sBLA 125408/351, V130_10 CSR Table 10-4, p. 85.

Reviewer comment: There were 9 concomitant infections (0.6%) in the QIVc arm and 2 (0.3%) in the QIV arm. Two individuals (one in each arm) were miscategorized and should have been categorized as forbidden vaccination or non-study vaccination. Thus, the rates of concomitant infections, all of which were laboratory confirmed influenza cases during the treatment period were 0.5% and 0.1% for QIVc and Afluria, respectively. These participants were excluded because the infection occurred prior to the follow-up blood draw, and as such, it is not clear if these are breakthrough cases or if these infants would not yet be considered fully immunized.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoints

For the primary analyses, the estimates and 95% CIs for the GMT ratios and SCR differences are presented in Table 5 and Table 6, respectively. With the upper limits of the 95% CIs < 1.5, all four strains met the pre-specified success criteria.

Success of the A/H3N2 hypothesis for the GMR is supported by the HAI results (CSR Table 14.2.1.1.1) using cell-derived targets, with

- QIVc GMT 288.1 (95% CI: 261.5, 317.5),
- Afluria GMT 227.6 (95% CI: 201.9, 256.6), and
- GMR 0.79 (95% CI: 0.69, 0.90).

Additionally, success of the A/H3N2 hypothesis for the SCR difference is also supported by the HAI results (CSR Table 14.2.2.1.1), with

- QIVc SCR 72.3% (95% CI: 69.5%, 74.9%),
- Afluria SCR 64.5% (95% CI: 60.5%, 68.5%), and
- SCR difference -7.8% (95% CI: -12.5%, -3.1%).

Reviewer comment: For both the GMRs and SCR differences, the HAI estimates of A/H3N2 immunogenicity using cell-derived targets were similar to the HAI based GMR and SCR difference estimates of the other three strains (A/H1N1, B/Yam, and B/Vic). Because the HAI measured immunogenicity is widely accepted, has pre-defined success criteria as a surrogate for disease, and would be more generalizable for comparison to other vaccines, I suggest making the HAI estimates for A/H3N2 available in the prescribing information (PI), in addition to the pre-defined MN estimates used to evaluate success. However, I defer to the clinical team for final determination.

For both endpoints (GMT and SCR), immunogenicity was higher when measured by HAI in comparison to the MN estimates for A/H3N2, though it is unclear how this would reflect effectiveness. In general, I defer to the clinical and assay reviewers for further discussion of the interpretation of the results from the two assay types.

Table 5: Postvaccination GMT and GMT Ratios, using Cell-derived Target Viruses (PPS)

Strain	QIVc N_{HAI}=1092 / N_{MN}=1078 (95% CI)	US-licensed QIV N_{HAI}=575 / N_{MN}=572 (95% CI)	US-licensed QIV over QIVc (95% CI)
A/H1N1	78.0 (70.8, 86.0)	57.3 (50.8, 64.6)	0.73 (0.65, **0.84**)
A/H3N2*	23.1 (21.2, 25.1)	23.9 (21.6, 26.6)	1.04 (0.93, **1.16**)
B/Yamagata	35.6 (32.9, 38.6)	26.0 (23.5, 28.6)	0.73 (0.66, **0.81**)
B/Victoria	22.4 (20.7, 24.2)	19.6 (17.8, 21.6)	0.88 (0.79, **0.97**)

Notes: Adjusted GMT and GMT ratio are presented, based on the model Log-transformed Postvaccination HAI (or MN) Titer = Vaccine + Age Strata + Gender + Vaccination History [y/n] + Log-transformed Prevaccination HAI (or MN) Titer + Site + Age Strata*Vaccine.

*The A/H3N2 strain is measured using the MN assay.

Source: sBLA 125408/351, V130_10 CSR Table 11-1, p. 92.

Table 6: SCR and SCR Differences, using Cell-derived Target Viruses (PPS)

Strain	QIVc (%) N_{HAI}=1092 / N_{MN}=1078 (95% CI)	US-licensed QIV (%) N_{HAI}=575 / N_{MN}=572 (95% CI)	US-licensed QIV (%)-QIVc (%) (95% CI)
A/H1N1	58.2 (55.3, 61.2)	46.8 (42.6, 51.0)	-11.5 (-16.4, **-6.4**)
A/H3N2*	27.6 (25.0, 30.4)	30.8 (27.0, 34.7)	3.1 (-1.4, **7.8**)
B/Yamagata	46.5 (43.5, 49.5)	31.7 (27.9, 35.6)	-14.9 (-19.6, **-10.0**)
B/Victoria	30.3 (27.6, 33.1)	24.4 (20.9, 28.1)	-6.0 (-10.3, **-1.4**)

*Note: The A/H3N2 strain is measured using the MN assay.
Source: sBLA 125408/351, V130_10 CSR Table 11-2, p. 95.

Reviewer comment: As seen in Table 5 and Table 6, the point estimate and the 95% CIs based on the A/H3N2 MN assays were less in favor of QIVc, whereas the results based on the A/H3N2 HAI assays indicates that QIVc was in favor (95% upper confidence limits were <1 for GMR and <0 for SCR difference). This may be explained in part by how the MN and HAI assays measure different types of antibodies. Thus, it is important to keep the type of assay in mind when interpreting the results. Nevertheless, the estimates above all support a conclusion that immunogenicity induced by QIVc is non-inferior to that induced by the Afluria.

6.1.11.2 Analyses of Secondary Endpoints

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

The estimates and 95% CIs for the GMT ratios and SCR differences are presented in Table 7 and Table 8, respectively. HAI estimates of immune response for the A/H3N2 strain are also included.

Table 7: Postvaccination GMT and GMT Ratios, using Egg-derived Target Viruses (PPS)

	Assay	QIVc N_{HAI}=1092 / N_{MN}=1079 (95% CI)	US-licensed QIV N_{HAI}=575 / N_{MN}=572 (95% CI)	US-licensed QIV over QIVc (95% CI)
A/H1N1	HAI	92.2 (83.6, 101.7)	82.9 (73.5, 93.6)	0.9 (0.8, 1.0)
A/H3N2	MN	43.4 (39.6, 47.5)	44.7 (40.0, 50.0)	1.0 (0.9, 1.2)
A/H3N2	HAI	115.0 (103.6, 127.7)	119.3 (104.9, 135.8)	1.0 (0.9, 1.2)
B/Yamagata	HAI	23.0 (21.2, 24.9)	24.7 (22.4, 27.3)	1.1 (1.0, 1.2)
B/Victoria	HAI	13.6 (12.6, 14.6)	14.8 (13.5, 16.2)	1.1 (1.0, 1.2)

Source: sBLA 125408/351, V130_10 CSR, Reviewer derived from Table 11-3, p. 100-101 and Table 14.2.1.1.3

Table 8: SCR and SCR Differences, using Egg-derived Target Viruses (PPS)

	Assay	QIVc (%) N_{HAI}=1092 / N_{MN}=1079 (95% CI)	US-licensed QIV (%) N_{HAI}=575 / N_{MN}=572 (95% CI)	US-licensed QIV (%) - QIVc (%) (95% CI)
A/H1N1	HAI	58.5 (55.5, 61.5)	56.0 (51.8, 60.1)	-2.5 (-7.5, 2.5)
A/H3N2	MN	37.4 (34.6, 40.4)	39.3 (35.3, 43.5)	1.9 (-3.0, 6.9)
A/H3N2	HAI	59.0 (56.1, 62.0)	58.1 (54.0, 62.2)	-1.0 (-6.0, 4.0)
B/Yamagata	HAI	38.6 (35.7, 41.6)	38.6 (34.6, 42.7)	0.0 (-4.9, 4.9)
B/Victoria	HAI	19.7 (17.4, 22.2)	20.9 (17.6, 24.4)	1.2 (-2.8, 5.4)

Source: sBLA 125408/351, V130_10 CSR, Reviewer derived from Table 11-3, p. 100-101 and Table 14.2.2.1.3

Additionally, percentage of HAI titer ≥ 1:10 and ≥ 1:40 were presented descriptively. These estimates were similar across arms.

The above analyses were repeated in FAS Immunogenicity, and there were no noticeable differences when compared to the PPS with respect to the endpoints of GMT, GMT ratio, GMR, seropositivity rates, percentage of subjects with titer≥1:40, SCR, and SCR difference, using egg-derived target viruses.

Reviewer comment: It is notable that the HAI-based results with a cell-derived target (Tables 5 and 6), where the 95% upper confidence limits (UCLs) were <1 for GMR and <0 for SCR difference (Section 6.1.11.1); whereas the HAI-based results (Tables 7 and 8) with an egg-derived target did not show the similar trend. Thus, the assay and derivation of the target strain should be considered in interpretation. I defer to the clinical and product reviewers for further interpretation of these differences. However, both sets of results clearly support the conclusion that the QIVc is non-inferior to Afluria across all four strains.

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

Estimates and 95% CIs in the PPS were presented in the primary immunogenicity analyses. There were no notable differences between the FAS Immunogenicity and the PPS with respect to the endpoints of GMT, GMT ratio, GMR, seropositivity rates, percentage of subjects with titer ≥1:40, SCR, and SCR difference, using cell-derived target viruses.

Secondary Objective 3: To describe the immunogenicity of QIVc and US-licensed QIV by MN assay with cell-derived targets for A/H1N1, B/Yamagata, and B/Victoria strains, in a subset of subjects

Because the MN assay is generally considered experimental, MN results were assessed in a randomly selected subset of participants. The GMT ratios were 0.77 (0.56, 1.06) for A/H1N1, 0.90 (0.71, 1.15) for B/Yamagata, and 0.85 (0.69, 1.05) for B/Victoria. The

SCR differences were -14.2% (-25.2%, -3.0%) for A/H1N1, -7.0% (-18.0%, 4.3%) for B/Yamagata, and -0.6% (-8.5%, 8.0%) for B/Victoria. At Day 29/57, percentages of subjects with titer ≥ 1:10 and ≥ 1:40 were similar across vaccine arms for each of the 3 strains.

6.1.11.3 Subpopulation Analyses

In addition to age group (6 to <24 months, 24 to <48 months), sex, and race subgroup analyses for the primary analyses, the applicant presented subgroup analyses for the prognostic factors such as pre-vaccination titer and previous influenza vaccine. Subgroup analyses for the primary endpoints are summarized below. Because the results for the HAI assay with the cell-derived target were also available for the A/H3N2 strain and are considered clinically relevant, they are also summarized by subgroup.

- By age group:

  Subgroup results by age are presented in Table 9 through Table 12. Overall, the results showed that the GMR and SCR difference results were mostly consistent across age groups. There were some slight differences for the A/H3N2 strain, which demonstrated a higher GMR in the older age group with the HAI and MN assays.

  Reviewer comment: Of note, the 6 to <24-month age group has not been previously studied, and the GMR and SCR results for this age group met the non-inferiority criteria. Efficacy of QIVc was previously evaluated in the 24 - < 48 months of age group as a subset of a larger pediatric trial (age 2-<18 years). The primary objective of this trial was to demonstrate the vaccine efficacy 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.

Table 9: Postvaccination GMT and GMT Ratios for Age 6-23 months, using Cell-derived Target Viruses (PPS)

Strain and Assay	QIVc N_{HAI}=366 / N_{MN}=360 (95% CI)	US-licensed QIV N_{HAI}=203 / N_{MN}=201 (95% CI)	US-licensed QIV over QIVc (95% CI)
A/H1N1 HAI	41.6 (35.2, 49.1)	35.0 (28.5, 42.9)	0.84 (0.67, 1.05)
A/H3N2 MN	17.3 (15.3, 19.5)	15.3 (13.2, 17.8)	0.89 (0.75, 1.04)
A/H3N2 HAI	188.2 (162.2, 218.5)	118.6 (98.7, 142.6)	0.63 (0.52, 0.77)
B/Yam HAI	24.6 (21.7, 28.0)	18.2 (15.5, 21.3)	0.74 (0.62, 0.88)
B/Vic HAI	17.0 (15.0, 19.1)	15.3 (13.2, 17.7)	0.90 (0.77, 1.06)

Source: sBLA 125408/351, V130_10 CSR, Calculated by Reviewer and verified using Tables 14.2.3.1.1.1 and 14.2.3.2.1.1

Table 10: Postvaccination GMT and GMT Ratios for Age 24-47 months, using Cell-derived Target Viruses (PPS)

Strain and Assay	QIVc N_{HAI}=726 / N_{MN}=718 (95% CI)	US-licensed QIV N_{HAI}=372 / N_{MN}=371 (95% CI)	US-licensed QIV over QIVc (95% CI)
A/H1N1 HAI	129.2 (115.5, 144.6)	84.4 (73.5, 97.0)	0.65 (0.56, 0.76)
A/H3N2 MN	29.8 (26.8, 33.1)	36.2 (31.8, 41.3)	1.22 (1.06, 1.40)
A/H3N2 HAI	376.9 (334.7, 424.4)	380.3 (328.5, 440.1)	1.01 (0.86, 1.18)
B/Yam HAI	48.6 (44.3, 53.3)	36.0 (32.1, 40.4)	0.74 (0.66, 0.84)
B/Vic HAI	28.3 (25.7, 31.0)	24.7 (22.0, 27.8)	0.88 (0.78, 0.99)

Source: sBLA 125408/351, V130_10 CSR, Calculated by Reviewer and verified using Tables 14.2.3.1.1.1 and 14.2.3.2.1.1

Table 11: SCR and SCR Differences for Age 6-23 months, using Cell-derived Target Viruses (PPS)

Strain and Assay	QIVc (%) N_{HAI}=366 / N_{MN}=360 (95% CI)	US-licensed QIV N_{HAI}=203 / N_{MN}=201 (95% CI)	US-licensed QIV over QIVc (95% CI)
A/H1N1 HAI	47.3 (42.1, 52.5)	36.9 (30.3, 44.0)	-10.32 (-18.54, -1.82)
A/H3N2 MN	18.3 (14.5, 22.7)	16.9 (12.0, 22.8)	-1.42 (-7.75, 5.44)
A/H3N2 HAI	70.5 (65.5, 75.1)	61.6 (54.5, 68.3)	-8.92 (-17.13, -0.85)
B/Yam HAI	39.3 (34.3, 44.6)	22.7 (17.1, 29.0)	-16.68 (-24.08, -8.81)
B/Vic HAI	24.3 (20.0, 29.0)	16.7 (11.9, 22.6)	-7.57 (-14.12, -0.52)

Source: sBLA 125408/351, V130_10 CSR, Calculated by Reviewer and verified using Tables 14.2.2.1.1.1 and 14.2.2.2.1.1

Table 12: SCR and SCR Differences for Age 24-47 months, using Cell-derived Target Viruses (PPS)

Strain and Assay	QIVc(%) N_{HAI}=726 / N_{MN}=718 (95% CI)	US-licensed QIV(%) N_{HAI}=372 / N_{MN}=371 (95% CI)	US-licensed QIV (%)- QIVc (%) (95% CI)
A/H1N1 HAI	63.8 (60.2, 67.3)	52.2 (46.9, 57.3)	-11.62 (-17.77, -5.46)
A/H3N2 MN	32.3 (28.9, 35.9)	38.3 (33.3, 43.4)	5.96 (0.01, 12.02)
A/H3N2 HAI	73.2 (69.8, 76.4)	66.1 (61.1, 70.9)	-7.04 (-12.90, -1.33)
B/Yam	50.1 (46.4, 53.8)	36.6 (31.7, 41.7)	-13.58 (-19.58, -7.40)
B/Vic	33.3 (29.9, 36.9)	28.5 (24.0, 33.4)	-4.84 (-10.45, 1.00)

Source: sBLA 125408/351, V130_10 CSR, Calculated by Reviewer and verified using Tables 14.2.2.1.1.1 and 14.2.2.2.1.1

- Sex

  In both the male and female subgroups, results of QIVc compared to Afluria were generally consistent in all four strains.

- Race

  Only the White and Black/African American subgroups had large enough sample sizes to evaluate the outcomes of interest. For each of the strains, results in both subgroups were similar to that in the overall population for all four strains.

- Pre-vaccination titer (<1:10 or >= 1:10)
  The GMRs and SCR differences between QIVc and Afluria were similar across all four strains for both pre-vaccination titer groups (<1:10 and >= 1:10). Of note, immune response was muted for the lower baseline titer group across all endpoints, assays, and target strains (e.g. the point estimates for GMTs were below 40 for both vaccines using the HAI assay; and HAI titers of 40 is a threshold generally considered protective).

- Previous influenza vaccination status
  The GMRs and SCR differences between QIVc and Afluria were similar across all four strains for both previously vaccinated and not previously vaccinated groups. SCRs were fairly similar across prior vaccination subgroups, but GMTs were slightly lower in the vaccine-naïve subgroup.

6.1.11.4 Dropouts and/or Discontinuations

As noted in Table 4, the PPS consisted of 71% and 74% of the FAS for the QIVc and Afluria arms, respectively, indicating a higher rate of loss to follow-up than planned in the protocol. Per the applicant, this was likely due to protocol deviations, which occurred in 27% of participants in the QIVc arm and 25% of participants in the Afluria arm. The most common major protocol deviation was a serology sample not being taken, reported by 17% and 15% of participants in the QIVc and Afluria arms, respectively.

In response to CBER request, the applicant conducted additional analyses to assess the robustness of the primary analyses in light of the unexpectedly high rate of missing data. In their response, the applicant clarified that most of the missingness in the PPS was due to either early termination before the second blood draw (9% and 7% for the QIVc and Afluria arms, respectively) or unavailable serology (17% and 14% for the QIVc and Afluria arms, respectively). Moreover, per the applicant, the unavailable serology results were due to the difficulty of sample collection in an infant population, rather than due to issues that might introduce bias in differential loss to follow-up, such as assay performance. FAS excluding the participants with missing serology was defined as FAS-Immunology.

The applicant also presented several additional arguments in support of the conclusion of non-inferiority in the PPS population:

- Baseline and demographic distributions were similar between FAS and FAS-Immunology, except for previous influenza vaccination, which made up a larger proportion of the FAS-Immunology than the FAS populations. However, this was balanced between arms, with previous vaccination making up 57.5% and 56.1% of the FAS-Immunology population, in the QIVc and Afluria arms, respectively.

- Baseline and demographic distributions were also similar between the participants with missing and non-missing data, with some allowance in variability due to the small sample sizes in the Afluria missing data group (n=157).
- GMT and SCR analyses were similar to the PPS population results when repeated in the FAS-Immunogenicity population, with no changes to the overall non-inferiority conclusion.
- For the GMT outcome, the applicant used pattern-mixture models with multiple imputation as a sensitivity analysis. Once imputed, analyses were based on the same model as in the original PPS. The QIVc missing data were imputed from 1) the available QIVc data and 2) the available Afluria data, for 100 replicates. For each replicate, the upper 95% CI was recorded, and the median and maximum of this empirical distribution were reported. Results were reported as median and maximum of the upper limit of the 95% CI for each source of missingness, across the four strains (see Table 13). Overall, the maximum upper limits of the 95% CIs were below 1.5 for all strains.

Table 13: Pattern-mixture model imputed maximums of upper 95% CIs

Strain	Assay type	FAS-Imm GMT 95% CI	PPS GMT 95% CI	PMM UCL Max* Afluria	PMM UCL Max* QIVc
A/H1N1	HAI	(0.62,0.80)	(0.64,0.84)	0.89	0.84
A/H3N2	HAI	(0.68,0.87)	(0.69,0.90)	0.97	0.89
A/H3N2	MN	(0.92,1.15)	(0.93,1.16)	1.20	1.19
B/Vic	HAI	(0.79,0.96)	(0.79,0.97)	1.02	1.02
B/Yam	HAI	(0.67,0.82)	(0.66,0.81)	0.89	0.85

*Note: PMM maximum GMT Ratio upper limit of the 95% CI from the 100 replicated imputations
Source: sBLA 125408/351.4, 1.11.3 Clinical Information Amendment, Table 1-1, p. 13. Received 07 June 2021.

- For the SCR outcome, the applicant performed a tipping point analysis where missing values were imputed across the full grid of possible outcomes. In other words, one scenario imputes all missing SCRs as a seroconversion success for Afluria and a seroconversion failure for QIVc, which is the extreme in an unfavorable result for QIVc. Alternatively, the extreme in favorable results for QIVc imputes all missing SCRs as a seroconversion success for QIVc and a seroconversion failure for Afluria. The conservative ITT analysis translates to imputing no success for all missing values in both arms. As seen in Section 6.1.11.1, SCR differences as measured by the HAI were in favor of QIVc. The tipping point analysis indicated that across the four strains, either no or only a few extreme imputation combinations resulted in analyses that would have failed non-inferiority, depending on the strain. For the MN measured A/H3N2 SCR difference, the tipping point was not as extreme but still indicated that a non-inferiority conclusion is likely robust for QIVc.

Reviewer comment: Based on the summary of demographic and baseline characteristics, there were no clear differences between the participants with missing and non-missing data that would suggest bias in favor of QIVc. The only noticeable difference was the larger proportion of previously vaccinated in the PPS group compared to FAS, though this was balanced across arm, suggesting this change is not due to vaccine. Though the

details are not clear on the PMM analysis, this analysis and the SCR tipping point analyses can be considered as additional supportive analyses that did not reveal evidence contradictory to the conclusion of non-inferiority.

6.1.11.5 Exploratory and Post Hoc Analyses

N/A

6.1.12 Safety Analyses

6.1.12.1 Methods

N/A

6.1.12.3 Deaths

There were two deaths during the study period, both in the QIVc arm. Neither event was considered to be associated with the study vaccines.

- A 9-month-old subject developed adenovirus encephalitis with a fatal outcome at (b) (6) days after second study vaccination.
- A 23-month-old subject suffered a fatal traffic accident.

6.1.12.4 Nonfatal Serious Adverse Events

Rates of serious adverse events (SAEs) were the same across vaccine arm (both arms 0.9%), and none were considered to be vaccine related. For solicited local adverse events after any vaccination, the rates of serious adverse events were 0.1-0.4% for induration, erythema, and ecchymosis in the QIVc arm and 0% in the Afluria arm. For tenderness, the rates of serious adverse events were slightly higher at 2.2% and 1.4% in the QIVc and Afluria arms, respectively. For solicited systemic adverse events after any vaccination, serious adverse event rates were similar across vaccine arm, with the highest rates being 2.1% and 1.4% for sleepiness in the QIVc and Afluria arms, respectively.

In the QIVc arm, 0.2% reported AEs leading to withdrawal from the study. In addition to the two subjects with fatal adverse events, there was one subject who withdrew after a seizure. No subjects in the Afluria group withdrew from the study because of an AE.

6.1.12.5 Solicited and Unsolicited Adverse Events

The rates of solicited AEs were similar between the QIVc and Afluria after any vaccination (64% and 66%, respectively), at 30 minutes after any vaccination (12% and 13%, respectively), and from Day 1 through Day 7 after any vaccination (60% and 63%, respectively). This also held true for any local and system AEs after any vaccination:

- At 30 minutes after any vaccination: Local (11% and 12%, for QIVc and Afluria, respectively) and Systemic (2% for both arms).
- Day 1 – Day 7 after any vaccination: Local (42% and 45%, for QIVc and Afluria, respectively) and Systemic (44% and 46%, respectively).

The rates for solicited AEs after vaccination 1 were similar for solicited AE rates after any vaccination.

Solicited AE rates after vaccination 2 were mostly lower:

- Any AE (47% for both arms).
- At 30 minutes after any vaccination: Any (8% for both arms), Local (7% and 8%, for QIVc and Afluria, respectively) and Systemic (1% for both arms).
- Day 1 – Day 7 after any vaccination: Any (44% for both arms), Local (25% and 26%, for QIVc and Afluria, respectively) and Systemic (34% and 32%, for QIVc and Afluria, respectively).

As in solicited AEs, unsolicited AE rates during the treatment period (Day 1 through Day 29/57) were similar across study arm, with 26% in both arms. Of these 4.4% and 4.5% were considered at least possibly related to the vaccine for QIVc and Afluria, respectively. The specific unsolicited AEs during this period were mostly balanced across arm, except for diarrhea which had 0.7% and 0.4% AE rates in QIVc and Afluria, respectively. No specific unsolicited AE during this period and possibly related to the vaccine was more than 1% in either arm.

6.1.12.6 Adverse Events of Special Interest (AESI)
Please refer to the clinical reviewer's memo.

6.1.12.7 Clinical Test Results

N/A

6.1.12.8 Dropouts and/or Discontinuations

For both arms, all enrolled patients were followed as part of the unsolicited and overall safety sets, and 98% of enrolled patients were followed as part of the solicited safety set. Thus, it is unlikely that there is dropout due to vaccine related adverse events.

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

Overall, non-inferiority was demonstrated for GMT ratio and SCR difference using the pre-specified HAI assay for the A/H1N1, B/Yam, and B/Vic strains and the pre-specified MN assay for the A/H3N2 strain, all with cell-derived target strains. The MN assay was selected to measure the primary endpoint for the A/H3N2 since the HAI assay failed to agglutinate in the prior season. However, this did not occur in the study season, and non-inferiority criteria were also met with the HAI assay with a cell-derived target. In addition, non-inferiority criteria were also met with egg-derived target strains. When stratified by age, the younger age group appeared to be less immunogenic than the older group; however, this occurred in both arms and did not change the conclusion of non-inferiority. It was also noted that those infants/toddlers with undetectable titers at baseline had a muted response; however, this effect was similar across arm.

There did not appear to be any differences in the safety profiles between the two study vaccines.

10.2 Conclusions and Recommendations

The immunogenicity induced by Flucelvax quadrivalent (QIVc) was demonstrated to be non-inferior to a currently approved QIV, Afluria. In particular, the immunogenicity of QIVc was non-inferior to Afluria in the lower age range of 6 to <24 months, an extension of the currently approved age range of 2 years of age and older. Flucelvax quadrivalent also demonstrated an acceptable safety profile in the infant and toddler population. There are no statistical concerns. Thus, I recommend an approval to extend the indication for QIVc to include the 6 to <24 months age range.