Application Type	BLA Supplement
STN	125254/642
CBER Received Date	October 31, 2016
PDUFA Goal Date	August 31, 2017
Division / Office	DVRPA /OVRR
Committee Chair	Timothy Fritz
Clinical Reviewer(s)	Cynthia Nolletti
Project Manager	Josephine Resnick
Priority Review	No
Reviewer Name(s)	Charles (Yin Kiu) Cheung
Review Completion Date / Stamped Date	
Supervisory Concurrence #1	Tsai-Lien Lin, Team Leader Viral and Bioassay Team, Vaccine Evaluation Branch, Division of Biostatistics
Supervisory Concurrence #2	Dale Horne, Branch Chief, Vaccine Evaluation Branch, Division of Biostatistics
Applicant	Seqirus Pty Ltd.
Established Name	Influenza Vaccine
(Proposed) Trade Name	Afluria® Quadrivalent
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Inactivated split virion, Quadrivalent Influenza Vaccine, 15 mcg hemagglutinin antigen for each of the four influenza strains recommended by the FDA VRBPAC for the 2015-2016 season
Dosage Form(s) and Route(s) of Administration	Intramuscular injection only, by needle and syringe (5 years of age and older) or by PharmaJet® Stratis® Needle-Free Injection System (18-64 years of age); administer as a single 0.5 mL dose
Dosing Regimen	1 or 2 doses at least 1 month apart (5-8 years); 1 dose (9 years and older)
Indication(s) and Intended Population(s)	Active immunization against influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine for use in persons 5 years of age and older.

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GLOSSARY

AE	Adverse events
AESI	Adverse events of special interest
CI	Confidence Interval
GMFI	Geometric Mean Fold Increase
GMT	Geometric Mean Titer
QIV	Quadrivalent Influenza Vaccine
RR	Relative Risk
SAE	Serious Adverse Events
SCR	Seroconversion Rate

1. EXECUTIVE SUMMARY

Seqirus (formerly bioCSL)'s Afluria Quadrivalent Influenza Vaccine (QIV) was approved on August 26th, 2016, for use in persons 18 years of age and older. In this BLA supplement, 125254/642, Seqirus is seeking approval to extend the indication of Afluria QIV from persons 18 years and older to persons 5 years and older. To support this proposed indication, the applicant submitted a clinical study report of a Phase 3 randomized, observer-blinded, controlled clinical trial conducted during the Northern Hemisphere 2015-2016 influenza season in children 5 through 17 years of age, in which Afluria QIV was compared to a US licensed QIV comparator (GSK's Fluarix). A total of 2278 subjects aged 5 through 17 years were included in the full analysis set.

The success criteria for all 8 co-primary immunogenicity endpoints for the 4 strains were met. Thus, Afluria QIV appears to elicit an immune response that was not inferior to that of the comparator QIV among this pediatric population.

The safety profiles of Afluria QIV and the comparator QIV appear to be comparable. No deaths, adverse events of special interests, or AEs leading to withdrawal were reported. Overall, 11 SAEs were reported in 8 subjects in the Afluria group (0.5%) and 2 SAEs were reported in 2 subjects in the comparator QIV group (0.4%). The proportions of subjects experiencing solicited and unsolicited adverse events between the Afluria QIV and comparator QIV groups were comparable. The observed proportions of subjects experiencing headache, malaise and fatigues, diarrhea, and fever were higher in the Afluria group than in the comparator QIV group in both the 5-8 and 9-17 years strata, with relative risk ranging from 1.16 to 2.80. However, their confidence intervals were wide and included 1. In the 9-17 year-old age stratum, the relative risk of myalgia was 1.50 (16.7% vs. 11.1%) with 95% CI of (1.03, to 2.19). In the 5-8 year-old cohort, the same trend for myalgia was not observed (9.8% in the Afluria QIV group and 11.3% in the comparator QIV group). I defer to the clinical reviewer to evaluate the acceptability of these safety results.

2. CLINICAL AND REGULATORY BACKGROUND

On August 26th, 2016, the FDA approved Seqirus (bioCSL)'s Afluria Quadrivalent Influenza Vaccine (QIV). This indication was approved under the BLA supplement 125254/565, based on the results from the clinical study CSLCT-QIV-13-01. This vaccine is indicated for active immunization against influenza disease caused by influenza A and B virus subtypes contained in the vaccine, for persons 18 years of age and older. In this BLA supplement, 125254/642, Seqirus is seeking the FDA's approval to expand the current indication for use in persons 5 years of age and older. To support this indication, Seqirus submitted results from the phase 3 randomized, observer-blinded, controlled clinical study CSLCT-QIV-13-02 conducted in 5-17 year-old subjects. Communications between Seqirus and CBER were documented in the Type B PreIND meeting minutes CRMTS#8832 PTS 1965 (April 1st, 2013), memo for IND 15974 CRMTS #9729 (May 12th, 2015), and Type B IND meeting summary IND 15974 CRMTS 10232 (May 11th, 2016).

The current package insert noted that Afluria's 2010 Southern Hemisphere trivalent influenza vaccine was associated with increased postmarketing reports of fever and febrile seizure in children predominantly below the age of 5 years as compared to previous years.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

The submission quality was adequate for conducting a statistical review.

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

NA

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

5.1 Review Strategy

I reviewed CSLCT-QIV-13-02. I verified the applicant's summary of primary immunogenicity endpoints (Figures 3 and 4) and associated subgroup analyses discussed in section 6.1.11.3, using the submitted immunogenicity dataset. In addition, I verified the applicant's main summary of adverse events (Table 4, Table 6, and tabulation of nonfatal serious adverse events), using the submitted safety dataset.

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

- BLA 125254/642.0 dated 10/31/2016
    - Module 5.3.5.1 Clinical Study Report CSLCT-QIV-13-02
- BLA 125254/642.3 dated 12/16/2016
    - Module 1.11.3 Efficacy Information Amendment

- BLA 125254/642.8 dated 4/21/2017
    - Module 1 Package Insert

5.3 Table of Studies/Clinical Trials

Final clinical study report CSLCT-QIV-13-02 was used to support the indication for children 5-17 years of age.

5.4 Consultations

NA

5.5 Literature Reviewed (if applicable)

NA

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

The applicant conducted a Phase 3 randomized, observer-blinded, active-controlled clinical trial during the Northern Hemisphere 2015-2016 influenza season in children 5 through 17 years of age.

6.1 Clinical Study CSLCT-QIV-13-02

6.1.1 Objectives and Endpoints

Objectives:

Primary immunogenicity objective:

- To demonstrate that vaccination with Afluria QIV elicits an immune response that is not inferior to that of a US-licensed comparator QIV containing the same virus strains as Afluria QIV, among a pediatric population 5 through 17 years of age.

Secondary immunogenicity objectives

- To characterize the immunogenicity of Afluria QIV and the US-licensed comparator QIV overall and in two age strata: 5-8 and 9-17 years.

Exploratory immunogenicity objective:

- To explore the association between the immune response after administration of Afluria QIV or the US-licensed comparator QIV by vaccine dose and baseline characteristics.

Secondary safety objective:

- To assess safety and tolerability of Afluria QIV, among children 5-17 years of age overall and in two age strata: 5-8 and 9-17 years of age.

Exploratory safety objective:

- To explore the association between any and severe grade fever (and potentially any other solicited systemic adverse events), after administration of Afluria QIV or the US-licensed comparator QIV by vaccine dose and baseline characteristics.

Endpoints:

Co-primary immunogenicity endpoints:

For each strain, 28 days after the last vaccination

- HI Geometric Mean Titer (GMT) ratios (comparator QIV over Afluria QIV)
- Difference between the Seroconversion Rates (SCR) (comparator QIV minus Afluria QIV)

Secondary Immunogenicity Endpoints:

For each strain,

- GMTs: Geometric mean of HI titers prevaccination (Day 1) and postvaccination (Study Exit Visit)
- SCRs: Percentage of subjects with either a prevaccination HI titer < 1:10 and a postvaccination HI titer ≥ 1:40, or a prevaccination titer ≥ 1:10 and a ≥ 4-fold increase in postvaccination titer
- The percentage of subjects with a titer ≥ 40 (seroprotection rates) at Day 1 and at Study Exit Visit
- Geometric mean fold increase (GMFI): Geometric mean fold titer rise of postvaccination HI antibody titer over the prevaccination HI antibody titer

Secondary Safety Endpoints:

- Solicited local reactions and systemic adverse events (AEs) through Day 7 after vaccination
- Cellulitis-like reaction for at least 28 days after each vaccination dose
- Unsolicited AEs for at least 28 days after each vaccination dose
- Serious adverse events (SAEs) for 180 days following the last study vaccination dose

6.1.2 Design Overview

Eligible subjects were stratified by age to one of two age cohorts: (A) subjects 5-8 years of age and (B) subjects 9-17 years of age. At least 50% of subjects were in cohort A.

After stratification, subjects were randomized using a 3:1 allocation ratio to receive either Afluria QIV or the US-licensed comparator QIV. Randomization was performed using an interactive response technology system.

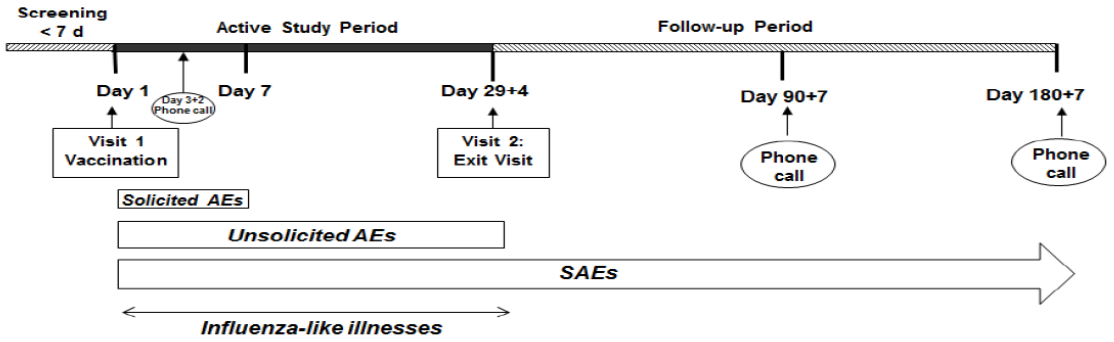
Vaccination:

Subjects were administered a 0.5mL intramuscular dose into either the right or left deltoid muscles, and received either 1 or 2 doses of Study Vaccine as clinically indicated, depending on their age on the day of first study vaccination and their previous history of

influenza virus vaccination. Vaccines were administered in accordance with the final published 2015-2016 influenza vaccination dose recommendations of the Advisory Committee on Immunization Practices (ACIP) for Prevention and Control of Seasonal Influenza with Vaccines. For 2015–2016, ACIP recommended that children aged 6 months through 8 years who have previously received ≥2 total doses of trivalent or quadrivalent influenza vaccine before July 1st, 2015 receive only 1 dose for 2015 – 2016, while children in this age group who have not previously received ≥2 doses of trivalent or quadrivalent influenza vaccine before July 1st, 2015 receive 2 doses for 2015–2016.

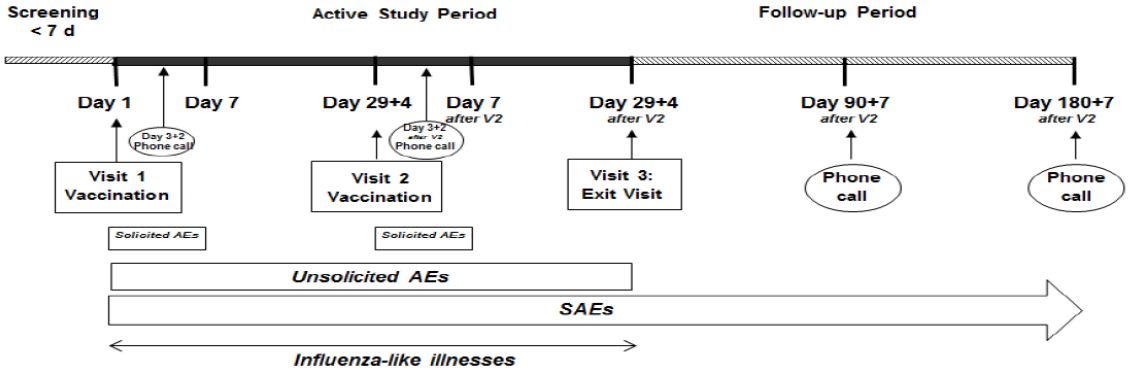
The study designs for one-dose and two-dose subjects are summarized in Figures 1 and 2.

Figure 1. Study design for one-dose subjects



Source: Figure 1 of the Final Clinical Study Report CSLCT-QIV-13-02

Figure 2. Study design for two-dose subjects



Source: Figure 2 of the Final Clinical Study Report CSLCT-QIV-13-02

The parent/guardian of subjects were to record in a Solicited Diary the occurrence of local and systemic symptoms and temperature between Day 1 and Day 7 following each vaccination. They were also instructed to record any unsolicited AEs and concomitant medication use that might have occurred between Day 1 and the Study Exit Visit in an Unsolicited /Concomitant Medications Diary.

6.1.3 Population

The study enrolled healthy male and female subjects 5 through 17 years of age in the United States of America. Eligibility and exclusion criteria were described in the protocol. Deviations from the protocol were noted in the final clinical study report, and the summary of populations for analyses was provided in Section 6.1.10.1.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The test vaccine was Afluria QIV. This product is a split-viron inactivated influenza virus vaccine, presented in a prefilled needleless syringe. Each 0.5 mL dose contained 15 mcg from each of the 4 influenza strains recommended by the FDA VRBPAC for the 2015-2016 influenza season in the US: A/California/7/2009 (H1N1)pdm09-like virus, A/Switzerland/9715293/2013 (H3N2)-like virus, B/Phuket/3073/2013-like virus (B/Yamagata lineage), and B/Brisbane/60/2008-like virus (B/Victoria lineage).

GlaxoSmithKline's Fluarix Quadrivalent was the comparator vaccine. This licensed product is a split-viron inactivated influenza virus vaccine, presented in a prefilled needleless syringe. Each 0.5 mL dose contained 15 mcg hemagglutinin antigen from each of the same four influenza strains as in the Afluria QIV vaccine.

6.1.6 Sites and Centers

The study was conducted in 32 centers in the USA.

6.1.7 Surveillance/Monitoring

The study used an independent Data Safety Monitoring Board (DSMB) to review safety data. The review, as defined in the DSMB Charter, was conducted after approximately one third of subjects in the 5 through 8 years age stratum had been enrolled. If halting rule criteria had been met in either study age cohort or ad-hoc review had been requested by Seqirus, analyses of safety data would have been triggered. Throughout the study, halting rules were not triggered.

6.1.8 Endpoints and Criteria for Study Success

The immunogenic noninferiority of Afluria QIV compared to the US-licensed comparator QIV was assessed by the 8 co-primary endpoints of HI geometric mean titer (GMT) and seroconversion rate (SCR) for four viral strains:

- The upper bound of the two-sided 95% confidence interval (CI) on the ratio of GMT (Comparator QIV/GMT Afluria QIV) ≤ 1.5
- The upper bound of the two-sided 95% CI on the difference between the SCRs (Comparator QIV minus GMT Afluria QIV) $\leq 10\%$

6.1.9 Statistical Considerations & Statistical Analysis Plan

Immunogenicity endpoints:
The GMT ratio was calculated for each strain separately. In the analysis of the co-primary endpoints, a generalized linear model (GLM) was fitted to the log-transformed postvaccination HI titer as the outcome variable against covariates (vaccine treatment, age stratum, sex, vaccination history, log-transformed baseline HI titer, site, and number of dose). GLMs with potential covariate interaction effects were also fitted. An adjusted difference in least-square means (on the log scale) was produced with 95% confidence limits. The estimated difference and the confidence limits were back-transformed to obtain the adjusted GMT ratio with 95% confidence limits. In the secondary analysis, unadjusted GMT ratios based on postvaccination GMTs were calculated.

All secondary immunogenicity endpoints were summarized overall and by subgroups: age strata, gender, race, and ethnicity.

The distribution of antibody titers 5 through 8 years of age, 9 through 17 years of age, as well as overall were displayed graphically using reverse cumulative distribution (RCD) curves. For the 5 through 8 years age stratum, separate RCD curves following the first and second vaccinations were displayed.

Safety endpoints:
The frequency and intensity of solicited and unsolicited AEs were summarized for each age and treatment group. The proportions of subjects reporting each type of AE were presented along with percentages and confidence intervals (CIs). Solicited local adverse reactions and systemic AEs were summarized by frequency, duration, and intensity. Unsolicited AEs were summarized by body system, intensity and relatedness to the Study Vaccine. All summaries were presented overall and by maximum intensity. Analyses by treatment group were repeated by age strata, gender, race, and ethnicity.

Sample size calculations:
The Afluria QIV was compared to the comparator QIV. The study was designed to achieve at least 80% power to demonstrate noninferiority for all 8 co-primary endpoints (4 for GMT ratio and 4 for SCR) using a one-sided alpha of 0.025.

For the SCR endpoint, the applicant assumed that the SCR for all strains for Afluria QIV was 50% and that there was no difference between Afluria QIV and the comparator QIV. For the GMT endpoint, the applicant assumed that there was no difference between Afluria QIV and the comparator QIV, and that the standard deviation of log titer was 1.4. Under these assumptions, with n=1500 in the Afluria QIV group and n=500 in the comparator QIV group, the overall power for 4 GMT ratio endpoints was 99.95% and the overall power for 4 SCR endpoints was 89.70%. Thus, the overall global power was 89.7% x 99.95% = 89.66%. Assuming 10% dropouts, N=2222 would be needed.

Reviewer's comment:

- *The study population used for evaluating immunogenicity (per-protocol population) had 1605 subjects in the Afluria QIV group and 528 subjects in the comparator group. The sample size was sufficient.*

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The Per-Protocol Population was the primary analysis population for the primary immunogenicity analysis.

Four safety populations were used to evaluate safety: overall safety population, solicited safety population, solicited safety population after the first vaccination, and the solicited safety population after the second vaccination.

Definitions:

- The Full Analysis Set (FAS) comprised all subjects who provided informed consent and who were randomized to treatment. Screening failures were not included in the FAS. However, the number of screening failures is summarized in the disposition tables, and all screening failures are listed.
- The Overall Safety Population comprised all subjects in the FAS who received at least one dose or partial dose of study vaccine and provided any evaluable follow-up safety data. A statement that there are no adverse events constituted follow-up safety data, provided a follow-up visit or safety phone call had taken place.
- The Solicited Safety Population comprised all subjects in the FAS who received at least one dose or partial dose of study vaccine and provided any evaluable data on solicited events.
- The Solicited Safety Population after the First Vaccination comprised all randomized subjects who received the first vaccination and provided any evaluable data on solicited events after the first vaccination.
- The Solicited Safety Population after the Second Vaccination comprised all randomized subjects who received the second vaccination and provided safety data on solicited events after the second vaccination.
- The Evaluable Population for immunogenicity analyses comprised all subjects in the FAS who:
    - received vaccine at Visit 1;
    - provided serology specimens which provided valid serology assay results from both Visit 1 and the Study Exit Visit (Visit 2 or 3);
    - did not experience a laboratory-confirmed influenza illness between Visit 1 and Study Exit Visit (Visit 2 or 3); and
    - did not receive any prohibited medication during the study that was medically assessed to potentially impact immunogenicity results.
- The Per-Protocol (PP) Population comprised all subjects in the Evaluable Population who did not have any protocol deviations that were medically assessed as potentially impacting on immunogenicity results.

Table 1 summarizes the number of subjects in each analysis population.

Table 1. Analysis populations by vaccine group.

Analysis Populations	Afluria QIV n (%)	Comparator QIV n (%)	Total (N=2278) n (%)
Full Analysis Population	1709 (100)	569 (100)	2278 (100)
Overall Safety Population	1692 (99.0)	560 (98.4)	2252 (98.9)
Solicited Safety Population	1621 (94.9)	535 (94.0)	2156 (94.6)
Solicited Safety Population After 1st Vaccination	1618 (94.7)	532 (93.5)	2150 (94.4)
Solicited Safety Population After 2nd Vaccination	178 (10.4)	63 (11.1)	241 (10.6)
Evaluable Population for immunogenicity	1622 (94.9)	533 (93.7)	2155 (94.6)
Per-Protocol Population	1605 (93.9)	528 (92.8)	2133 (93.6)

Source: Table 11.1-1 from the Final Clinical Study Report CSLCT-QIV-13-02

6.1.10.1.1 Demographics

The demographics and baseline characteristics appear to be comparable between the Afluria QIV and Comparator QIV groups (Table 2).

Table 2. Demographics and Baseline Characteristics of the Full Analysis Set

	Afluria QIV (n=1709)	Comparator QIV (n=569)	Total (N=2278)
Age (years)			
Mean (SD)	9.5 (3.49)	9.5 (3.46)	9.5 (3.48)
Age Group (%)			
5 through 8 years	875 (51.2)	291 (51.1)	1166 (51.2)
9 through 17 years	834 (48.8)	278 (48.9)	1112 (48.8)
Gender (%)			
Male	884 (51.7)	302 (53.1)	1186 (52.1)
Female	825 (48.3)	267 (46.9)	1092 (47.9)
Ethnicity (%)			
Hispanic or Latino	412 (24.1)	130 (22.8)	542 (23.8)
Not Hispanic or Latino	1293 (75.7)	438 (77.0)	1731 (76.0)
Not Reported	2 (0.1)	1 (0.2)	3 (0.1)
Unknown	2 (0.1)	0	2 (<0.1)
Race (%)			
American Indian/Alaska Native	5 (0.3)	2 (0.4)	7 (0.3)
Asian	16 (0.9)	2 (0.4)	18 (0.8)
Black or African American	359 (21.0)	113 (19.9)	472 (20.7)
Native Hawaiian or Other Pacific Islander	13 (0.8)	2 (0.4)	15 (0.7)
White	1239 (72.5)	430 (75.6)	1669 (73.3)
Other	77 (4.5)	20 (3.5)	97 (4.3)
Weight (kg) Mean (SD)	41.32 (21.517)	41.32 (21.521)	41.32 (21.513)
Prevaccination Oral Temp (°C) Mean	36.72	36.72	36.72

Source: Table 11.2-1 from the Final Clinical Study Report CSLCT-QIV-13-02

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
NA

6.1.10.1.3 Subject Disposition
Please refer to section 6.1.11.4.

6.1.11 Efficacy Analyses

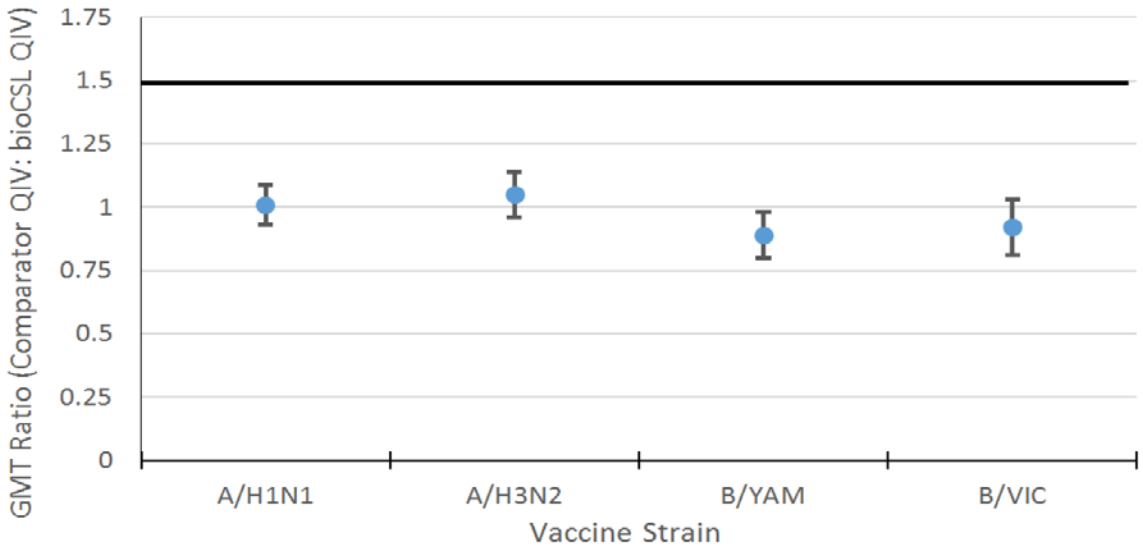
6.1.11.1 Analyses of Primary Endpoint(s)

The GMT ratios (comparator QIV over Afluria QIV) and differences in SCRs (comparator QIV minus Afluria QIV) for the 4 influenza subtypes from clinical study CSLCT-QIV-13-02 on subjects 5-17 years of age were the co-primary endpoints of the study (Figures 3 and 4). The upper confidence limit of each endpoint was below its non-inferiority margin. Thus, the success criteria of the study were met.

Reviewer's comment:

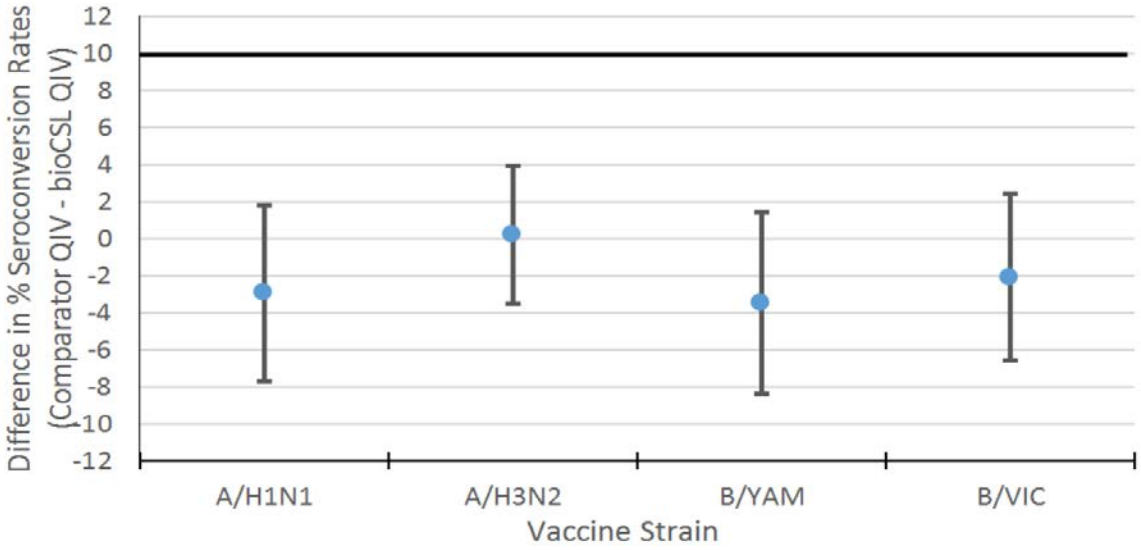
- *I verified the applicant's results.*

Figure 3. The estimates of GMT ratio (95% CI) of subjects 5-17 years of age, for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria.



The bold horizontal line represents the margin of noninferiority for GMT ratio (1.5).
Source: Figure 1 of the sponsor's Final Clinical Study Report CSLCT-QIV-13-02 on page 16.

Figure 4. Difference in SCR of subjects 5-17 years of age, for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria.



The bold horizontal line represents the margin of noninferiority for the difference in SCR(10%).
Source: Figure 2 of the sponsor's Final Clinical Study Report CSLCT-QIV-13-02 on page 17.

6.1.11.2 Analyses of Secondary Endpoints

The postvaccination GMT, geometric mean fold increase, seroconversion rate, and % subjects with postvaccination titer ≥ 40 were comparable between the two vaccine groups, for each age stratum and subjects 5-17 years old overall. The percentages of subjects with postvaccination titer ≥40 were high for all strains, across treatment and age strata (≥ 98.9% for A/H1N1 and A/H3N2, ≥ 86.6% for B/Victoria, and ≥ 69.1% for B/Yamagata). The seroconversion rates of all subjects 5 through 17 years of age in the Afluria QIV group were the highest for A/H3N2 (≥ 82.9%), followed by B/Victoria (≥ 72.1%), A/H1N1 (≥ 66.4%), and B/Yamagata (≥ 58.5%). For A/H1N1, the prevaccination titers of the subjects in the Alfuria QIV group were already high (≥81.2% of the overall prevaccination subjects had titer ≥ 40).

6.1.11.3 Subpopulation Analyses

For all antigens, the immune responses between vaccine groups were comparable across sex, race, and ethnicity (Hispanic/non-Hispanic) strata. For race, only the "Whites" and "Blacks" had enough subjects to perform a meaningful subgroup analysis.

Age strata:

- The GMTs and SCRs appear to be comparable between the Afluria QIV and comparator QIV groups for subjects 5 through 8 years old and for subjects 9 through 17 years old (Tables 11.4-2 and 11.4-3 of the Final Clinical Study Report CSLCT-QIV-13-02).

Sex:

- For each of the male and female subgroups, the GMTs and SCRs appear to be comparable between the two vaccine groups, for each of the 4 strains (Tables 14.2.1.3 and 14.2.2.3 from the Additional tables submitted to BLA 125254/642.3).

Race/Ethnicity:

- For race, only the "White" and "Black or African American" subgroups had over 20 subjects. The GMTs and SCRs appear to be comparable between Afluria QIV and comparator QIV, for these two subgroups (Tables 14.2.1.4 and 14.2.2.4 from the Additional tables submitted to BLA 125254/642.3).
- For ethnicity, the applicant evaluated the "Hispanic or Latino" and "Not Hispanic or Latino" subgroups. The GMTs and SCRs appear to be comparable between Afluria QIV and comparator QIV, for these two subgroups (Tables 14.2.1.5 and 14.2.2.5 from the Additional tables submitted to BLA 125254/642.3).

Reviewer's comment:

- *I verified the applicant's results of subpopulation analyses.*

6.1.11.4 Dropouts and/or Discontinuations

Reasons for discontinuation were summarized (Table 3). The majority of discontinued subjects were lost to follow-up. The percentages of discontinued subjects were similar between the two vaccine groups.

Table 3. Subject Disposition (Per-Protocol Population and Reasons for Discontinuation)

	Afluria QIV		**Comparator QIV**		**Overall**	
	n	(%)	n	(%)	n	(%)
Per-Protocol Population						
Included	1605	(93.9)	528	(92.8)	2133	(93.6)
Excluded	104	(6.1)	41	(7.2)	145	(6.4)
Completed Study	1628	(95.3)	535	(94.0)	2163	(95.0)
Discontinued from Study	81	(4.7)	34	(6.0)	115	(5.0)
Ongoing	0		0		0	
Reasons for discontinuation						
Adverse Event(s)	0		0		0	
Death	0		0		0	
Lost to Follow-up	67	(3.9)	25	(4.4)	92	(4.0)
Other	2	(0.1)	1	(0.2)	3	(0.1)
Investigator Decision	3	(0.2)	0		3	(0.1)
Major Protocol Deviation	0		0		0	
Study Terminated by Sponsor	0		0		0	
Withdrawal by Subject	9	(0.5)	8	(1.4)	17	(0.7)

Source: Table 14.1.1.1 from the Final Clinical Study Report CSLCT-QIV-13-02

6.1.12 Safety Analyses

Solicited Adverse Events

The proportions of subjects experiencing each type of solicited adverse event in the Afluria QIV and comparator QIV groups appear to be comparable.

5-8 years old

- Local adverse reactions were experienced by 57.2% of the Afluria QIV recipients and 54.0% of the comparator QIV recipients (Table 4). For each type of local adverse reaction, the proportions in the two groups appear to be generally comparable. Pain was the most common local adverse reaction.
- Systemic adverse events were experienced by 27.6% of the Afluria QIV recipients and 26.3% of the comparator QIV recipients. Headache and myalgia were the most common systemic adverse events. The relative risks comparing the Afluria QIV and comparator QIV groups were the highest for malaise and fatigue (1.51; 95% CI=[0.89, 2.55]), diarrhea (1.22; 95% CI=[0.62, 2.43]), and fever (1.22; 95% CI=[0.62, 2.43]).

9-17 years old

- Local adverse reactions were experienced by 54.2% of the Afluria QIV recipients and 50.2% of the comparator QIV recipients (Table 4). For each type of local adverse reaction, the rates of the two treatment groups appeared to be generally comparable. Pain was the most common local adverse reaction.
- Systemic adverse events were experienced by 34.1% of the Afluria QIV recipients and 28.7% of the comparator QIV recipients. Headache and myalgia were the most common systemic adverse events. The relative risks comparing the Afluria QIV and Comparator QIV groups were the highest for fever (2.80; 95% CI=[0.65, 12.04]), but the confidence interval is wide. For myalgia, the relative risk of myalgia was 1.50; 95%CI=[1.03, 2.19]. The relative risk of malaise and fatigue, headache, and diarrhea were 1.30 (95% CI=[0.81, 2.08]), 1.29 (95% CI=[0.93, 1.79]), and 1.29 (95%CI=[0.67, 2.46]), respectively.

Reviewer's comment:

- *Across both 5-8 years old and 9-17 years old cohorts, the Afluria QIV group had higher proportions of subjects experiencing headache, malaise and fatigue, diarrhea, and fever than the comparator QIV group. However, given the current sample sizes, the confidence intervals of these relative risk estimates were relatively wide and covered the value 1. For the 9-17 years old cohort, the proportion of subjects experiencing myalgia was higher in the Afluria QIV group (16.7%) than in the comparator QIV group (11.1%) (Relative Risk=1.50; 95% CI = [1.03, 2.19]). However, in the 5-8 years old cohort, the same trend for myalgia was not observed (9.8% in the Afluria QIV group and 11.3% in the comparator QIV group).*

Table 4. Proportion of subjects per age cohort with any solicited local adverse reactions or systemic adverse events within 7 days after administration of Afluria QIV or comparator QIV

	Percentage (%) of subjects in each Age Cohort Reporting an Event							
	Subjects 5 through 8 years				Subjects 9 through 17 years			
	Afluria QIV N=829		Comparator QIV N=274		Afluria QIV N=792		Comparator QIV N=261	
	Any	Gr3	Any	Gr3	Any	Gr3	Any	Gr3
Local Adverse Reactions[a]								
Any	57.2	5.5	54.0	4.0	54.9	3.2	50.2	3.8
Pain	51.3	0.8	49.6	0.7	51.5	0.3	45.2	0.4
Redness	19.4	3.5	18.6	1.8	14.8	1.9	16.1	1.9
Swelling/Lump	15.3	3.4	12.4	2.2	12.2	2.0	10.7	1.9
Systemic Adverse Events[b]								
Any	27.6	1.6	26.3	1.5	34.1	1.4	28.7	0.8
Headache	12.3	0.1	10.6	0.4	18.8	0.4	14.6	0.4
Myalgia	9.8	0.1	11.3	0.4	16.7	0.3	11.1	0.4
Malaise and Fatigue	8.8	0.4	5.8	0	10.0	0.4	7.7	0
Nausea	7.1	0.1	8.4	0	7.7	0	8.0	0
Diarrhea	5.2	0	3.6	0	5.4	0	4.2	0
Fever	4.5	1.2	3.6	0.7	2.1	0.5	0.8	0
Vomiting	2.4	0.2	4.4	0	1.8	0	2.3	0

Source: Tables 12.2.2-1, 12.2.2-2, 12.2.2-3, and 12.2.2-4 of the Final Clinical Study Report CSLCT-QIV-13-02
Abbreviations: Gr 3, Grade 3; Comparator, Comparator quadrivalent influenza vaccine (Fluarix® Quadrivalent [GlaxoSmithKline Biologicals])
a. Local adverse reactions: Grade 3 pain is that which prevents daily activity; Swelling/Lump and redness: any = ≥ 0mm diameter, Grade 3 = ≥ 30mm diameter.
b. Systemic adverse events: Fever: any = ≥ 100.4°F, Grade 3 = ≥ 102.2°F; Grade 3 for all other adverse events is that which prevents daily activity.

Cellulitis-like reaction:
One subject who received Afluria QIV experienced cellulitis-like reaction. The investigator later confirmed the reaction was not cellulitis.

Unsolicited Adverse Events:
Unsolicited adverse events were experienced by 15.9% of the subjects in the Afluria QIV group and 12.5% in the comparator QIV group (Table 5). Cough, pyrexia (fever), and oropharyngeal pain were the most common unsolicited adverse events (Table 6). The percentages of subjects experiencing these adverse events appear to be comparable between the vaccine groups.

Table 5. Unsolicited Adverse Events (≥ 1% of Subjects in any Vaccine Group) by Maximum Intensity in the Overall Safety Population

	Afluria QIV N=1692 (%)	Comparator QIV N=560 (%)	Overall N=2252 (%)
Percentage of subjects experiencing one or more unsolicited adverse events	15.9	12.5	15.1
- Grade 1 (mild)	8.8	5.5	8.0
- Grade 2 (moderate)	6.4	5.9	6.3
- Grade 3 (severe)	0.7	1.1	0.8
Percentage of subjects with one or more related unsolicited adverse events	3.8	2.0	3.4
- Grade 1 (mild)	2.5	0.9	2.1
- Grade 2 (moderate)	1.1	0.9	1.0
- Grade 3 (severe)	0.1	0.2	0.1

Source: Table 12.2.2-5 from the Final Clinical Study Report CSLCT-QIV-13-02

Table 6. Unsolicited Adverse Events (≥ 1% of Subjects in any Vaccine Group) by Preferred Term in the Overall Safety Population

	Afluria QIV N=1692 (%)	Comparator QIV N=560 (%)	Overall N=2252 (%)
Upper respiratory tract infection	1.1	0.5	0.9
Ear pain	0.2	1.1	0.4
Cough	2.1	2.0	2.0
Oropharyngeal pain	1.3	1.4	1.3
Rhinorrhea	0.9	1.1	0.9
Vomiting	0.8	1.4	1.0
Pyrexia	1.3	1.6	1.4

Source: Table 12.2.2-5 from the Final Clinical Study Report CSLCT-QIV-13-02

Safety Subgroup analyses:
The percentages of subjects experiencing each type of solicited adverse event appear to be comparable in the Afluria QIV and comparator QIV groups for each age stratum, gender, race, and ethnicity (Tables 14.3.1.1.2 – 14.3.1.1.5, 14.3.1.2.2, 14.3.1.2.5 – 14.3.1.2.7 in the Final CSR).

6.1.12.1 Methods

Please refer to section 6.1.9.

6.1.12.3 Deaths

No deaths were reported in this study.

6.1.12.4 Nonfatal Serious Adverse Events

A total of 13 Serious Adverse Events (SAEs) were reported in 10 subjects. Eleven SAEs were reported in 8 subjects (0.5%) in the Afluria QIV group, and 2 SAEs were reported in 2 subjects (0.4%) in the comparator QOV group.

In the Afluria QIV group, the 11 SAEs reported are 1 count (<0.1%) of attention deficit/hyperactive disorder, bipolar disorder, femur fracture, pancreatic injury, gastritis viral, psychotic disorder, influenza, abdominal pain, suicidal ideation, and 2 counts (<0.1%) of depression. One subject has attention deficit/hyperactive disorder and bipolar disorder, one subject has 2 counts of depression, and one subject has gastritis viral and psychotic disorder.

In the comparator QIV group, the 2 SAEs reported are suicide attempt (0.2%) and spontaneous abortion (0.2%).

One case of influenza B infection in the Afluria QIV recipient was assessed by the applicant as meeting the criteria for vaccine failure. The other cases were considered to be unrelated to the study vaccines.

6.1.12.5 Adverse Events of Special Interest (AESI)

Several AESI were monitored: Bell's palsy, demyelinating disorders, encephalomyelitis, Guillain-Barré syndrome, optic neuritis, transverse myelitis, thrombocytopenia, and vasculitis. No AESI were reported in this study.

6.1.12.6 Clinical Test Results

NA

6.1.12.7 Exploratory Safety Analyses

An exploratory safety objective was to evaluate whether there is an association between any and severe grade fever and baseline characteristics, after administration of Afluria QIV or the comparator QIV. A multiple logistic regression model was fitted with occurrence of
(severe) fever as the outcome variable and number of doses (1 or 2), age strata, gender, weight (above or below median weight), and vaccinated against influenza in the previous year (yes/no) as covariates. No significant associations were observed between the occurrence of fever or the occurrence of severe fever with any of the covariates.

6.1.12.7 Dropouts and/or Discontinuations

No subjects discontinued due to adverse events.

7. INTEGRATED OVERVIEW OF EFFICACY

NA

8. INTEGRATED OVERVIEW OF SAFETY

NA

9. ADDITIONAL STATISTICAL ISSUES

NA

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Immunogenicity:
A total of 8 co-primary immunogenicity endpoints (4 GMT ratios and 4 SCRs) were used to evaluate the immune response against 4 influenza subtypes. The upper confidence limit of each endpoint was below its non-inferiority margin. Thus, the success criteria of the study were met.

Safety:
Overall, the safety profiles of Afluria QIV and the comparator QIV appear to be comparable. However, I made the following note:

- Across both 5-8 years old and 9-17 years old cohorts, the Afluria QIV group had higher percentages of subjects experiencing headache, malaise and fatigue, diarrhea, and fever than the comparator QIV group. However, given the current sample sizes, the confidence intervals of these relative risk estimates were relatively wide and included the value 1. For the 9-17 years old cohort, the percentage of subjects experiencing myalgia was higher in the Afluria QIV group (16.7%) than in the comparator QIV group (11.1%) (Relative Risk=1.50; 95% CI = [1.03, 2.19]). However, in the 5-8 years old cohort, the same trend was not observed (9.8% in the Afluria QIV group and 11.3% in the comparator QIV group).

10.2 Conclusions and Recommendations

Based on the results of immunogenicity and safety data generated in clinical study CSLCT-QIV-13-02, the Afluria QIV vaccine appears to be acceptable for use in persons 5 - 17 years of age.