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Application Type	BLA Supplement
STN	125254/692
CBER Received Date	November 1, 2017
PDUFA Goal Date	September 1, 2018
Division / Office	DVRPA /OVRR
Committee Chair	Josephine Resnick
Clinical Reviewer(s)	Cynthia Nolletti
Project Manager	Helen Gemignani Timothy Fritz
Priority Review	No
Reviewer Name(s)	Rong Fu
Review Completion Date / Stamped Date	
Supervisory Concurrence	Tsai-Lien Lin Team Leader, Bioassay & Viral Team, VEB/DB/OBE
	Lihan Yan Acting Branch Chief, VEB/DB/OBE
Applicant	Seqirus Pty Ltd.
Established Name	Influenza Vaccine
(Proposed) Trade Name	Afluria Quadrivalent, Influenza Vaccine
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Each 0.5 mL dose contains 15µg hemagglutinin from each of the recommended influenza types and subtypes: A/H1N1, A/H3N2, B/Yamagata, and B/Victoria.
Dosage Form(s) and Route(s) of Administration	Sterile suspension for intramuscular injection.
Dosing Regimen	One 0.5 mL dose (persons ≥9 years); one or two 0.5 mL doses (based on prior vaccination history) at least 1 month apart (persons 36 months through 8 years); one or two 0.25 mL doses (based on prior vaccination history) at least 1 month apart (persons 6 through 35 months).
Indication(s) and Intended Population(s)	Active immunization against influenza disease caused by influenza virus present in vaccine for use in persons 6 months of age and older.

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GLOSSARY

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
AESI	Adverse Event of Special Interest
CSR	Clinical Study Report
FAS	Full Analysis Set
GLM	General Linear Model
GMFI	Geometric Mean Fold Increase
GMT	Geometric Mean Titer
HA	Hemagglutinin Antigen
HI	Hemagglutination Inhibition
IM	Intramuscular(ly)
PPP	Per-Protocol Population
QIV	Quadrivalent Influenza Vaccine
RR	Relative Risk
SAE	Serious Adverse Event
SCR	Seroconversion Rate
SPR	Seroprotection Rate

1. EXECUTIVE SUMMARY

Seqirus's Afluria Quadrivalent Influenza Vaccine (QIV) is currently approved for use in persons 5 years of age and older. In this BLA supplement, Seqirus submitted the clinical study report (CSR) of study CSLCT-QIV-15-03, a phase 3 randomized, observer-blinded, comparator controlled clinical trial to evaluate the immunogenicity and safety of Afluria Quadrivalent in the pediatric population 6 months through 59 months of age, and sought approval for an indication for use of Afluria Quadrivalent (referred to as Seqirus QIV in this review) in persons 6 months of age and older.

Study CSLCT-QIV-15-03 was conducted primarily to demonstrate non-inferior immunogenicity of Seqirus QIV to that of a US-licensed comparator QIV in children 6 months through 59 months of age as measured by post-vaccination Hemagglutination Inhibition (HI) antibody geometric mean titers (GMTs) and seroconversion rates (SCRs). The non-inferiority criteria for all 8 co-primary immunogenicity endpoints (GMT ratios and SCR differences for 4 influenza viral strains contained in the study vaccines) were met. In addition, no notable safety concerns were identified comparing Seqirus QIV to Comparator QIV. I recommend approval of Afluria Quadrivalent for use in children 6 months through 59 months of age.

2. CLINICAL AND REGULATORY BACKGROUND

Seqirus's Afluria QIV was approved for use in persons 18 years of age and older on August 26, 2016 (BLA 125254/565). An indication extension to persons 5 years of age and older was approved on August 31, 2017 (BLA 125254/642). In this BLA supplement, Seqirus submitted the final CSR of study CSLCT-QIV-15-03, conducted during the Northern Hemisphere 2016-2017 influenza season to evaluate the immunogenicity and

safety of Afluria Quadrivalent in the pediatric population 6 months through 59 months of age, and sought approval for use of Afluria Quadrivalent in persons 6 months of age and older. The primary objective of study CSLCT-QIV-15-03 was to demonstrate that vaccination with Seqirus QIV elicits an immune response that is not inferior to the US-licensed comparator QIV containing the same virus strains as Seqirus QIV among children 6 months through 59 months of age.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review.

3.2 Compliance With Good Clinical Practices And Data Integrity

Please refer to the clinical and bioresearch and monitoring reviews.

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

Please refer to each corresponding discipline review.

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

5.1 Review Strategy

This review focuses on the immunogenicity and safety objectives of study CSLCT-QIV-15-03. The submitted data, protocol, statistical analysis plan, and CSR were reviewed.

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

This review is primarily based on the documents (CSR, protocol, and statistical analysis plan) and data submitted to Module 5.3.5.1 of BLA 125254/692.

5.3 Table of Studies/Clinical Trials

This submission included one clinical study CSLCT-QIV-15-03.

5.4 Consultations

NA

5.5 Literature Reviewed (if applicable)

NA

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study CSLCT-QIV-15-03

Title: A Phase 3, Randomized, Multicenter, Observer-blinded, Noninferiority Study to Evaluate the Immunogenicity and Safety of a Quadrivalent Inactivated Influenza Virus Vaccine (Seqirus QIV) with a US-licensed Quadrivalent Inactivated Comparator Influenza Virus Vaccine (Comparator QIV) in a Pediatric Population 6 Months Through 59 Months of Age

6.1.1 Objectives

Primary Objective:

- To demonstrate that vaccination with Seqirus QIV elicits an immune response that is not inferior to the US-licensed comparator QIV (Comparator QIV) containing the same virus strains as Seqirus QIV among a pediatric population 6 months through 59 months of age.

Secondary Objectives:

- To assess the safety and tolerability of Seqirus QIV, in two age strata: 6 months through 35 months, and 36 months through 59 months, as well as overall;
- To characterize the immunogenicity of Seqirus QIV and the US-licensed comparator QIV in two age strata: 6 months through 35 months, and 36 months through 59 months, as well as overall.

6.1.2 Design Overview

This phase 3 study was a randomized, observer-blinded, and comparator controlled clinical trial conducted during the 2016-2017 Northern Hemisphere influenza immunization season in male and female subjects 6 months through 59 months of age. The planned enrollment was 2222 subjects, who were randomized at a ratio of 3:1 to receive Seqirus QIV or Comparator QIV (Fluzone Quadrivalent). The randomization was stratified by age cohort (Cohort A: 6 through 35 months of age; Cohort B: 36 through 59 months of age) with no more than 60% of the total sample size represented in each age cohort. Subjects received either one or two doses (29 days apart) of the study vaccine (Seqirus QIV or Comparator QIV) depending on their previous history of influenza vaccination and according to the US Advisory Committee on Immunization Practices (ACIP) 2016-2017 pediatric influenza dosing recommendations.

6.1.3 Population

The study enrolled male and female subjects 6 through 59 months of age at the time of first vaccination and born between 36 and 42 weeks of gestation in generally good health.

6.1.4 Study Treatments or Agents Mandated by the Protocol

- Cohort A: Subjects 6 through 35 months of age received one or two 0.25 mL doses of study vaccine by intramuscular (IM) injection according to the US ACIP dosing recommendations for the 2016-2017 influenza season.

- Cohort B: Subjects 36 through 59 months of age received one or two 0.5 mL doses of study vaccine by IM injection according to the US ACIP dosing recommendations for the 2016-2017 influenza season.

For both study vaccines, each 0.25 mL dose contained 7.5 mcg hemagglutinin antigen (HA) and each 0.5 mL dose contained 15 mcg HA from each of the following four influenza strains recommended by FDA's VRBPAC for the 2016-2017 season: A/California/7/2009 (H1N1) pdm09-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus, B/Brisbane/60/2008-like virus (B/Victoria lineage), and B/Phuket/3073/2013-like virus (B/Yamagata lineage).

6.1.6 Sites and Centers

The study was conducted in 39 centers in the US.

6.1.7 Surveillance/Monitoring

Blood samples were collected at Visit 1 (Day 1) and Study Exit Visit (approximately 29 days post the last vaccination) for measurements of HI antibody titers. Safety monitoring included solicited local reactions and systemic adverse events (AEs) for 7 days following each study vaccination recorded in a 7-day diary, unsolicited AEs for at least 28 days following the last study vaccination recorded in an Other Body Symptoms Diary, and cellulitis-like reactions (defined as concurrent presence of all three of the following: Grade 3 injection site pain, Grade 3 injection site erythema, and Grade 3 injection site induration) for at least 28 days following the last study vaccination. Monitoring of serious adverse events (SAEs) and AEs of special interest (AESIs) continued for 180 days following the last study vaccination.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint:

The primary objective was assessed by 8 co-primary endpoints of post-vaccination (Study Exit Visit) HI GMT and SCR for each viral strain contained in the vaccines. The SCR was defined as the percentage of subjects with either a pre-vaccination HI titer <1:10 and a post-vaccination HI titer ≥1: 40, or a pre-vaccination HI titer ≥1:10 and a ≥4-fold increase in post-vaccination HI titer.

- Non-inferiority criteria: Seqirus QIV was to be considered non-inferior to the Comparator QIV for each strain if:
    - the upper bound of the two-sided 95% confidence interval (CI) on the ratio of the GMTs (Comparator QIV /Seqirus QIV) ≤1.5; and
    - the upper bound of the two-sided 95% CI on the difference between the SCRs (Comparator QIV – Seqirus QIV) ≤10%.

Secondary Safety Endpoints:

- Frequency and severity of solicited local reactions and systemic AEs for 7 days after each vaccination dose;
- Frequency of cellulitis-like reactions for at least 28 days after each vaccination dose;
- Frequency and severity of unsolicited AEs for at least 28 days after each vaccination dose;

- Frequency of SAEs for at least 180 days after the last vaccination dose.

Secondary Immunogenicity Endpoints:
The humoral immune response was assessed in terms of HI antibodies for both Seqirus QIV and Comparator QIV. Serum HI antibody titers against the four influenza vaccine strains were used to calculate:

- GMT at Day 1 and Study Exit Visit;
- SCR;
- Seroprotection rate (SPR), defined as the percentage of subjects with a titer ≥1:40, at Day 1 and Study Exit Visit;
- Geometric Mean Fold increase (GMFI) from Day 1 to Study Exit Visit.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Immunogenicity Analysis on the Primary Objective:
To determine the GMT ratio, a general linear model (GLM) was fitted on log transformed post-vaccination HI titer as the outcome variable and with inclusion of covariates of treatment group, pre-vaccination HI titer, age cohort, sex, influenza vaccine received prior year, number of doses, study site, and age-by-vaccine interaction. The interaction term was removed from the fit of the model if assessed to be not significant. From the model an adjusted difference in least-square means (on the log scale) was estimated with the 95% CI, which were back transformed to obtain an adjusted GMT ratio with the 95% CI. The adjusted GMT ratios and CIs were used for the non-inferiority assessment. Each of the four strains was analyzed separately. If all 8 co-primary endpoints resulted in a conclusion of non-inferiority, then the overall non-inferiority of Seqirus QIV compared to the Comparator QIV was to be concluded. The CI for the difference in SCRs were calculated by the exact method.

Safety Analysis:
Safety endpoints were analyzed descriptively by tabulating the incidence rates by treatment group overall and for each age cohort. Relative risks (RRs) were calculated for solicited AEs comparing the Seqirus QIV to the Comparator QIV.

Changes in the Conduct of the Study and Planned Analyses:
The CIs for RRs on safety endpoints were computed using the asymptotic method, rather than the exact method as planned, as the low frequency of events would cause the time of computation of exact CIs to be extremely extended.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

- The Full Analysis Set (FAS) comprised all subjects who provided informed consent and who were randomized to treatment. The FAS was used to produce summaries and listings of subject characteristics.
- The Overall Safety Population comprised all subjects in the FAS who received at least one dose or partial dose of Study Vaccine and had provided any evaluable

follow-up safety data (i.e., any safety information recorded for a subject in a study diary or in the subject's medical notes). The safety population was used to produce summaries and listings of all safety data.

- 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 subjects in FAS 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 subjects in FAS who received the second vaccination and provided any evaluable 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, had valid serology assay results from both Visit 1 and the Study Exit Visit, did not experience a laboratory-confirmed influenza illness between Visit 1 and Study Exit Visit, and did not receive any prohibited medication during the study that was medically assessed to potentially impact immunogenicity results.
- The Per-Protocol Population (PPP) comprised all subjects in the Evaluable Population who did not have any protocol deviations that were medically assessed as potentially impacting on immunogenicity results. The PPP was the primary population for the immunogenicity analyses.

6.1.10.1.1 Demographics

There were no notable differences in the distribution of demographic and baseline characteristics between the two treatment groups in the FAS or within the age strata. Overall, there were slightly more male subjects (51.6%) than female subjects (48.4%). The majority of subjects were white (71.0%). Subjects of black or African American origin constituted 21.5% of subjects overall. The overall mean age of all subjects was 36.6 months (6 through 35 months age cohort: 21.7 months; 36 through 59 months age cohort: 47.1 months). For subjects in the FAS, 74% reported having received an influenza vaccine in the past, and 50.7% reported having received an influenza vaccine in the previous 2015/2016 Northern Hemisphere Season.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

NA

6.1.10.1.3 Subject Disposition

A total of 2339 subjects were screened, and 89 of them were screen failures. Among 2250 subjects who were randomized to study treatment, 3 were excluded from the clinical database and FAS due to not having valid Information Consent and being randomized in error prior to obtaining Informed Consent. Therefore, the FAS included 2247 subjects who gave Informed Consent and were randomized to treatment (1684 subjects randomized to Seqirus QIV and 563 subjects randomized to Comparator QIV). Among them, 7 subjects did not receive any study vaccinations. Table 1 displays the details on the analysis set allocation.

For the 252 subjects in the FAS who were excluded from the Evaluable Population for immunogenicity analyses, the most common reason for exclusion was missing either pre- and/or post-vaccination serology assay results (N=218). Of the 1995 subjects in the Evaluable Population, 55 had protocol deviations medically assessed as potentially affecting the immunogenicity results, and thus were excluded from the PPP; therefore, the PP Population included 1940 subjects.

Table 1: Number of Subjects in Each Analysis Population

	Seqirus QIV N (%)	Comparator QIV N (%)	Overall N (%)
FAS	1684	563	2247
Overall Safety Population	1673 (99.3)	559 (99.3)	2232 (99.3)
Solicited Safety Population	1618 (96.1)	545 (96.8)	2163 (96.3)
Solicited Safety Population After 1st Vaccination	1609 (95.5)	544 (96.6)	2153 (95.8)
Solicited Safety Population After 2nd Vaccination	551 (32.7)	185 (32.9)	736 (32.8)
Evaluable Population Included in the immunogenicity analyses	1492 (88.6)	503 (89.3)	1995 (88.8)
Per-Protocol Population	1456 (86.5)	484 (86.0)	1940 (86.3)

Percentages were based on the number of subjects in the FAS in the respective group assigned at randomization.
Source: Table 14.1.1.1 of the CSR

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The noninferiority criterion for the GMT ratio (adjusted analysis) in subjects 6 through 59 months of age was met for each strain contained in Seqirus QIV. The upper bounds of the two-sided 95% CIs of the GMT ratios (Comparative QIV/Seqirus QIV) did not exceed 1.5 for all strains (Table 2).

Table 2: Post-vaccination HI Antibody GMTs and Analyses of Noninferiority of Seqirus QIV Relative to Comparator QIV for Each Strain 28 Days after Last Vaccination Among a Pediatric Population 6 through 59 months of Age (Per-Protocol Population)

Strain	Adjusted GMT Seqirus QIV (N=1455[a])	Adjusted GMT Comparator QIV (N = 484[b])	GMT ratio[c] (Comparator QIV / Seqirus QIV) (95% CI)
A/H1N1	353.5	281.0	0.79 (0.72, 0.88)
A/H3N2	393.0	500.5	1.27 (1.15, 1.42)
B/Yamagata	23.7	26.5	1.12 (1.01, 1.24)
B/Victoria	54.6	52.9	0.97 (0.86, 1.09)

[a] Subject (b) (6) was excluded from the adjusted GMT analysis for all strains as the subject did not have information on pre-vaccination history. For A/H3N2, N=1454: subject (b) (6) had missing A/H3N2 post-vaccination titer.
[b] For B/Victoria, N=483: subject (b) (6) had missing B/Victoria pre-vaccination titer.
[c] Adjusted analysis model: Log-transformed Post-Vaccination HI Titer=Vaccine + Age Strata + Sex + Prior Year Vaccination History [y/n] + Log-transformed Pre-Vaccination HI Titer + Site + Number of Doses (1 vs 2) + Age Strata*Vaccine. The Age Strata*Vaccine interaction term maintained only in the model for B/Victoria as the interaction result was significant ($p<0.05$).
Source: Table 14.2.1.1 of the CSR

Reviewer's comments:

*The age*vaccine interaction in the regression model for B/Victoria was significant, indicating differential treatment effect on HI titers between age cohorts. Therefore, I performed a subgroup analysis on B/Victoria by age cohort to further explore the*

treatment effect in each age cohort. The subgroup analysis results showed that the upper bound of the two-sided 95% CI of the GMT ratio (Comparator QIV/Seqirus QIV) did not exceed 1.5 in either age cohort (6 months through 35 months: 0.82 [95% CI: 0.69, 0.98)]; 36 months through 59 months: 1.13 [95% CI: 0.96, 1.33)], which was consistent in conclusion with the analysis in the overall pediatric population 6 through 59 months of age.

The noninferiority criterion for the difference in SCRs in subjects 6 through 59 months of age was met for each strain contained in Seqirus QIV. The upper bounds of the two-sided 95% CIs of the SCR differences (Comparator QIV – Seqirus QIV) did not exceed 10% for all strains (Table 3).

Table 3: Post-vaccination HI Antibody SCRs and Analyses of Noninferiority of Seqirus QIV Relative to Comparator QIV for Each Strain 28 Days after Last Vaccination Among a Pediatric Population 6 through 59 months of Age (Per-Protocol Population)

Strain	SCR (95% CI) Seqirus QIV (N=1456[a])	SCR (95% CI) Comparator QIV (N = 484[b])	SCR Difference (Comparator QIV - Seqirus QIV) (95% CI)
A/H1N1	79.1 (76.9, 81.1)	68.8 (64.5, 72.9)	−10.3 (−15.4, -5.1)
A/H3N2	82.3 (80.2, 84.2)	84.9 (81.4, 88.0)	2.6 (−2.5, 7.8)
B/Yamagata	38.9 (36.4, 41.4)	41.9 (37.5, 46.5)	3.1 (−2.1, 8.2)
B/Victoria	60.2 (57.6, 62.7)	61.1 (56.6, 65.4)	0.9 (−4.2, 6.1)

[a] For A/H3N2, N=1455: subject (b) (6) had missing A/H3N2 post-vaccination titer.
[b] For B/Victoria, N=483: subject (b) (6) had missing B/Victoria pre-vaccination titer.
Source: Table 14.2.2.1 of the CSR

All 8 co-primary endpoints fulfilled the noninferiority criteria; therefore, the overall noninferiority of Seqirus QIV compared to Comparator QIV was concluded.

6.1.11.2 Analyses of Secondary Endpoints

The secondary immunogenicity objective of the study was to characterize the immunogenicity of Seqirus QIV and Comparator QIV in the two age cohorts as well as overall. Table 4 and Table 5 summarize unadjusted GMTs and SCRs at the Study Exit Visit by age cohort and overall. Post-vaccination GMTs were higher in the older than in the younger age cohort, and higher for the A strains than for the B strains in both age cohorts. The SCRs tended to be higher in the older than in the younger age cohort for the B strains, lower in the older than in the younger age cohort for A/H1N1, and similar between two age cohorts for A/H3N2.

Table 4: Post-Vaccination HI Antibody GMTs by Age Cohort and Overall (Per-Protocol Population)

Strain	6 through 35 months		36 through 59 months		Overall	
	Seqirus QIV (N=586[a])	Comparator QIV (N=193)	Seqirus QIV (N=870)	Comparator QIV (N=291)	Seqirus QIV (N=1456[b])	Comparator QIV (N=484)
A/H1N1	184.9	168.3	590.2	469.2	370.0	311.7
A/H3N2	184.9	247.5	778.6	1047.0	436.8	589.1
B/Yamagata	15.6	16.3	35.4	44.1	25.5	29.7
B/Victoria	39.8	31.9	72.1	85.9	56.8	57.9

[a] For A/H3N2, N=585: subject (b) (6) had missing A/H3N2 post-vaccination titer.
[b] For A/H3N2, N=1455: subject (b) (6) had missing A/H3N2 post-vaccination titer.
Source: Table 14.2.3.1 and Table 14.2.3.2 of the CSR

Table 5: Post-Vaccination HI Antibody SCRs by Age Cohort and Overall (Per-Protocol Population)

Strain	6 through 35 months		36 through 59 months		Overall	
	Seqirus QIV (N=586[a])	Comparator QIV (N=193)	Seqirus QIV (N=870)	Comparator QIV (N=291[b])	Seqirus QIV (N=1456[c])	Comparator QIV (N=484[d])
A/H1N1	81.9 (78.6, 84.9)	80.3 (74.0, 85.7)	77.1 (74.2, 79.9)	61.2 (55.3, 66.8)	79.1 (76.9, 81.1)	68.8 (64.5, 72.9)
A/H3N2	82.4 (79.1, 85.4)	85.0 (79.1, 89.7)	82.2 (79.5, 84.7)	84.9 (80.2, 88.8)	82.3 (80.2, 84.2)	84.9 (81.4, 88.0)
B/Yamagata	22.5 (19.2, 26.1)	26.9 (20.8, 33.8)	49.9 (46.5, 53.3)	51.9 (46.0, 57.8)	38.9 (36.4, 41.4)	41.9 (37.5, 46.5)
B/Victoria	52.9 (48.8, 57.0)	49.7 (42.5, 57.0)	65.1 (61.8, 68.2)	68.6 (62.9, 73.9)	60.2 (57.6, 62.7)	61.1 (56.6, 65.4)

[a] For A/H3N2, N=585: subject (b) (6) had missing A/H3N2 post-vaccination titer.
[b] For B/Victoria, N=290: subject (b) (6) had missing B/Victoria pre-vaccination titer.
[c] For A/H3N2, N=1455: subject (b) (6) had missing A/H3N2 post-vaccination titer.
[d] For B/Victoria, N=483: subject (b) (6) had missing B/Victoria pre-vaccination titer.
Source: Table 14.2.5.1 and Table 14.2.5.2 of the CSR

6.1.11.3 Subpopulation Analyses

Analyses of HI antibody titers by sex did not demonstrate notable differences between males and females in both treatment groups (results not presented).

Race or ethnicity subgroups apart from "White" or "Black or African American" race, and "Hispanic or Latino" or "Not Hispanic or Latino" ethnicity had a sample size too small for a meaningful comparison.

- The post-vaccination HI GMTs and SCRs were generally similar for Hispanic or Latino subjects compared to Not Hispanic or Latino subjects for all strains in both treatment groups (results not presented).
- The post-vaccination HI GMTs were generally higher in the Black or African American subjects compared to White subjects for all strains in both treatment groups. The post-vaccination HI GMTs tended to be higher in the Comparator QIV group than in the Seqirus QIV group for A/H3N2 in race groups (Table 6).
- The SCRs were generally similar or greater in the Seqirus QIV group compared to the Comparator QIV group for all strains in both race groups (Table 7).

Table 6: Post-Vaccination HI Antibody GMTs by Race (Per-Protocol Population)

Strain	White		Black or African American	
	Seqirus QIV (N=1062)	Comparator QIV (N=343)	Seqirus QIV (N=302)	Comparator QIV (N=100)
A/H1N1	330.8	278.4	513.0	439.2
A/H3N2	397.2	504.6	542.5	963.4
B/Yamagata	23.8	27.0	30.2	39.1
B/Victoria	56.1	56.0	57.5	69.2

Source: Table 14.2.3.4 of the CSR

Table 7: Post-Vaccination HI Antibody SCRs by Race (Per-Protocol Population)

Strain	White		Black or African American	
	Seqirus QIV (N=1062)	Comparator QIV (N=343[a])	Seqirus QIV (N=302)	Comparator QIV (N=100)
A/H1N1	78.5 (75.9, 81.0)	71.1 (66.0, 75.9)	79.5 (74.5, 83.9)	57.0 (46.7, 66.9)
A/H3N2	81.5 (79.1, 83.8)	88.9 (85.1, 92.0)	84.8 (80.2, 88.6)	74.0 (64.3, 82.3)
B/Yamagata	36.3 (33.4, 39.2)	40.5 (35.3, 45.9)	44.0 (38.4, 49.8)	50.0 (39.8, 60.2)
B/Victoria	57.9 (54.9, 60.9)	59.6 (54.2, 64.9)	67.2 (61.6, 72.5)	62.0 (51.7, 71.5)

[a] For A/H3N2, N=342: subject (b) (6) had missing A/H3N2 post-vaccination titer.
Source: Table 14.2.5.4 of the CSR

6.1.11.4 Dropouts and/or Discontinuations

For subjects in the FAS, 93% of them completed the study, with a similar percentage in both treatment groups. The most common reason for discontinuation was lost to follow-up (Table 8).

Table 8: Distribution of Subjects Who Completed the Study and Reasons for Discontinuation (Full Analysis Set)

	Seqirus QIV (N=1684)	Comparator QIV (N=563)	Overall (N=2247)
Completed Study	1566 (93.0)	521 (92.5)	2087 (92.9)
Discontinued from Study	118 (7.0)	42 (7.5)	160 (7.1)
Reasons for discontinuation			
Lost to Follow-up	84 (5.0)	29 (5.2)	113 (5.0)
Withdrawal by Subject	26 (1.5)	10 (1.8)	36 (1.6)
Other	4 (0.2)	1 (0.2)	5 (0.2)
Investigator Decision	3 (0.2)	1 (0.2)	4 (0.2)
Major Protocol Deviation	1 (0.1)	1 (0.2)	2 (0.1)

Source: Table 14.1.1.1 of the CSR

6.1.11.5 Exploratory and Post Hoc Analyses

NA

6.1.12 Safety Analyses

6.1.12.1 Methods

Solicited AEs

The number and percentage of subjects reporting any solicited local and systemic AEs within 7 days after any vaccination are presented in Table 9 for subjects 6 through 35 months of age and in Table 10 for subjects 36 through 59 months of age. In each age cohort, all solicited local adverse reactions and systemic AEs were reported at lower frequencies after the second vaccination than after the first vaccination with Seqirus QIV. Generally, there were no notable differences in the proportions of subjects reporting solicited local or systemic AEs comparing Seqirus QIV to Comparator QIV in both age cohorts, except that the Seqirus QIV group tended to have a lower incidence rate of fever than the Comparator QIV group among subjects 6 through 35 months of age. Smaller proportion of subjects receiving Seqirus QIV in the younger age cohort experienced solicited local adverse reactions than in the older age cohort (32.9% versus 44.8%), whereas greater proportion of subjects in the younger age cohort experienced solicited systemic AEs (48.9% versus 32.2%). It should be noted, however, that different systemic AEs were collected in the two age cohorts – two most common solicited systemic AEs in the younger age cohort (irritability and loss of appetite) were not collected in the older age cohort.

Table 9: Number and Proportion[a] of Subjects with Solicited Local Adverse Reactions or Systemic Adverse Events within 7 Days after Vaccination, Subjects 6 through 35 months (Solicited Safety Population)

	Seqirus QIV (N= 669)		Comparator QIV (N= 227)	
	n (%)		n (%)	
	Any	Gr 3	Any	Gr 3
Local Adverse Reactions	220 (32.9)	5 (0.7)	78 (34.4)	6 (2.7)
Pain	139 (20.8)	1 (0.1)	58 (25.6)	1 (0.4)
Redness	139 (20.8)	4 (0.6)	40 (17.6)	4 (1.8)
Swelling	41 (6.1)	3 (0.4)	14 (6.2)	2 (0.9)
Systemic Adverse Events	327 (48.9)	21 (3.1)	113 (49.8)	9 (4.0)
Irritability	220 (32.9)	5 (0.7)	64 (28.2)	1 (0.4)
Diarrhea	162 (24.2)	1 (0.1)	58 (25.6)	1 (0.4)
Loss of Appetite	134 (20.0)	2 (0.3)	44 (19.4)	1 (0.4)
Nausea and/or vomiting	63 (9.4)	5 (0.7)	25 (11.0)	0 (0.0)
Fever	48 (7.2)	17 (2.5)	27 (11.9)	6 (2.6)

Gr 3 = Grade 3

[a] Proportion (%) was derived from the number of subjects that reported the event divided by the number of subjects in the Solicited Safety Population with non-missing data for each age cohort, treatment group, and each solicited parameter.

Source: Table 14.3.1.2.2 and Table 14.3.1.3.2.1 of the CSR

Table 10: Number and Proportion[a] of Subjects with Solicited Local Adverse Reactions or Systemic Adverse Events within 7 Days after Vaccination, Subjects 36 through 59 months (Solicited Safety Population)

	Seqirus QIV (N= 949)		Comparator QIV (N= 318)	
	n (%)		n (%)	
	Any	Gr 3	Any	Gr 3
Local Adverse Reactions	425 (44.8)	26 (2.7)	130 (40.9)	18 (5.7)
Pain	337 (35.5)	0 (0.0)	100 (31.4)	2 (0.6)
Redness	213 (22.4)	22 (2.3)	66 (20.8)	17 (5.3)
Swelling	96 (10.1)	16 (1.7)	41 (12.9)	8 (2.5)
Systemic Adverse Events	306 (32.2)	19 (2.0)	102 (32.1)	5 (1.6)
Diarrhea	115 (12.1)	1 (0.1)	28 (8.8)	2 (0.6)
Malaise and Fatigue	136 (14.3)	5 (0.5)	42 (13.2)	1 (0.3)
Myalgia	94 (9.9)	1 (0.1)	30 (9.4)	0 (0.0)
Headache	59 (6.2)	4 (0.4)	16 (5.0)	0 (0.0)
Nausea and/or vomiting	87 (9.2)	4 (0.4)	21 (6.6)	1 (0.3)
Fever	46 (4.8)	11 (1.2)	19 (6.0)	3 (0.9)

Gr 3 = Grade 3

[a] Proportion (%) was derived from the number of subjects that reported the event divided by the number of subjects in the Solicited Safety Population with non-missing data for each age cohort, treatment group, and each solicited parameter.

Source: Table 14.3.1.2.2 and Table 14.3.1.3.2.1 of the CSR

Unsolicited AEs from Day 1 through Day 28 Following Any Vaccination

Unsolicited AEs, Grade 3 unsolicited AEs, related unsolicited AEs, and Grade 3 related unsolicited AEs were reported in similar proportions of subjects in the Seqirus QIV group and the Comparator QIV group (Table 11). The majority of subjects in the Seqirus QIV group with at least one unsolicited AEs reported events with a maximum intensity of mild or moderate.

In the Seqirus QIV group, the proportion of subjects reporting any unsolicited AEs was higher in the younger age cohort (37.6%) compared to the older age cohort (28.1%); the proportion of subjects reporting any Grade 3 unsolicited AEs was slightly higher in the younger age cohort (3.7%) compared to the older age cohort (1.9%).

Table 11: Summary of Unsolicited Adverse Events within 28 Days after Vaccination (Safety Population)

	6 through 35 months		36 through 59 months		Overall	
	Seqirus QIV (N=694)	Comparator QIV (N = 233)	Seqirus QIV (N=979)	Comparator QIV (N = 326)	Seqirus QIV (N=1673)	Comparator QIV (N = 559)
Any unsolicited AE	261 (37.6)	88 (37.8)	275 (28.1)	83 (25.5)	536 (32.0)	171 (30.6)
Grade 3 unsolicited AE	26 (3.7)	7 (3.0)	19 (1.9)	7 (2.1)	45 (2.7)	14 (2.5)
Related unsolicited AE	66 (9.5)	25 (10.7)	76 (7.8)	27 (8.3)	142 (8.5)	52 (9.3)
Related Grade 3 unsolicited AE	4 (0.6)	2 (0.9)	0 (0.0)	3 (0.9)	4 (0.2)	5 (0.9)

Source: Table 14.3.1.9.1.2, Table 14.3.1.9.4.2, Table 14.3.1.9.2.2, Table 14.3.1.9.3.2, Table 14.3.1.9.5.2, and Table 14.3.1.9.6.2 of the CSR

Cellulitis-like Reaction

One subject who received Comparator QIV in the 36 through 59 months age cohort experienced a local cellulitis-like reaction during the study on Day 2 after the second vaccination. The reaction was assessed by the Investigator and confirmed not to be cellulitis.

6.1.12.3 Deaths

There were no deaths reported during the study.

6.1.12.4 Nonfatal Serious Adverse Events

A total of 14 subjects (11 in the Seqirus QIV group [0.7%] and 3 in the Comparator QIV group [0.5%]) reported a total of 15 SAEs during the study. No SAEs were assessed as related to the study vaccine by the Investigator. All SAEs were reported by subjects in the 6 through 35 months age cohort, except one (Humerus fracture) by a subject receiving Comparative QIV in the 36 through 59 months age cohort.

6.1.12.5 Adverse Events of Special Interest (AESI)

There were two AESIs of febrile convulsion reported between the Study Exit Visit and Final Database Lock in two subjects (0.1%) receiving Seqirus QIV aged 6 through 35 months. Neither of the events was assessed as related to the study vaccine by the Investigator.

6.1.12.6 Clinical Test Results

NA

6.1.12.7 Dropouts and/or Discontinuations

No subject discontinued the study due to an AE or SAE.

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

Study CSLCT-QIV-15-03 was conducted primarily to demonstrate non-inferior immunogenicity of Seqirus QIV to that of a US-licensed comparator QIV in children 6 through 59 months of age as measured by post-vaccination HI antibody GMTs and SCRs. The non-inferiority criteria for all 8 co-primary immunogenicity endpoints (GMT ratio and SCR difference for 4 influenza viral strains contained in the study vaccines) were met.

- The HI GMT ratio (Comparator QIV/Seqirus QIV) and 95% CI for each of the four strains (A/H1N1, A/H3N2, B/Yamagata, and B/Victoria) were 0.79 (0.72, 0. 88), 1.27 (1.15, 1.42), 1.12 (1.01, 1.24), and 0.97 (0.86, 1.09), respectively (criterion: upper CI bound $\leq$1.5).
- The HI SCR difference (%) (Comparator QIV-Seqirus QIV) and 95% CI for each of the four strains (A/H1N1, A/H3N2, B/Yamagata, and B/Victoria) were -10.3 (-15.4, -5.1), 2.6 (-2.5, 7.8), 3.1 (-2.1, 8.2), and 0.9 (-4.2, 6.1), respectively (criterion: upper CI bound $\leq$10%).

In addition, no notable safety concerns were identified comparing Seqirus QIV to Comparator QIV.

10.2 Conclusions and Recommendations

I recommend approval of Afluria Quadrivalent for use in children 6 through 59 months of age.