

Summary Basis for Regulatory Action

Date: October 3, 2018

From: Josephine S. Resnick, PhD, Review Committee Chair

BLA STN#: 125254/692

Applicant Name: Seqirus Pty Ltd.

Date of Submission: October 31, 2017

Goal Date: December 1, 2018

ProprietaryName: Afluria® Quadrivalent

Indication: Afluria® Quadrivalent (Afluria QIV) is approved for use in patients 5 years of age and older for the prevention of influenza disease caused by influenza virus types A and B contained in the vaccine. This supplement includes safety and effectiveness data for the use of Afluria Quadrivalent in persons 6 through 59 months of age.

Recommended Action:

The Review Committee recommends approval of this product.

Review Office Signatory Authority: Marion Gruber, PhD, Division Director, OVR, CBER

- I concur with the summary review.
- I concur with the summary review and include a separate review to add further analysis.
- I do not concur with the summary review and include a separate review.

The table below indicates the material reviewed when developing the SBRA

Document title	Reviewer name, Document date
CMC Review <ul style="list-style-type: none">• CMC (OVR/DVP)• Facilities Review (OCBQ/DMPQ)	Falko Schmeisser, PhD – July 5, 2018 Nicole Li – April 27, 2018
Clinical Reviews <ul style="list-style-type: none">• Clinical (OVR/DVRPA)• Postmarketing safety epidemiological review (OBE/DE)	Cynthia Nolletti, MD – September 7, 2018 Wenyu Sun, MD – September 26, 2018 Carla Jordan – August 17, 2018

<ul style="list-style-type: none"> • <i>Bioresearch Monitoring (OCBQ/DIS)</i> 	
Statistical Reviews <ul style="list-style-type: none"> • <i>Clinical data (OBE/DB)</i> • <i>HAI Assay (OBE/DB)</i> 	Rong Fu, PhD – June 19, 2018; August 19, 2018 (Addendum) Rong Fu, PhD – June 19, 2018
Labeling Reviews <ul style="list-style-type: none"> • <i>OVRP/DVRPA</i> • <i>OVRP/DVRPA</i> 	Daphne Stewart – September 11, 2018 Helen Gemignani – August 30, 2018
Other Review <ul style="list-style-type: none"> • <i>Labeling Consult Review (OCBQ/APLB)</i> 	Sonny Saini, PharmD – March 16, 2018

1. INTRODUCTION

Influenza viruses are responsible for seasonal epidemics and periodic pandemics that can cause substantial morbidity and mortality, particularly among the very young (persons less than 5 years of age), elderly (persons greater than 65 years of age), and those with pre-existing conditions. Outbreaks of influenza are responsible for significant burdens on the healthcare system and can have major economic implications. Annual vaccination against influenza A subtype and type B viruses is the most effective method to reduce the risk of disease, especially in at-risk groups. The Advisory Committee on Immunization Practices (ACIP) recommends annual influenza vaccination for healthy individuals aged 6 months of age and older.

Afluria® Quadrivalent (Afluria QIV) is an influenza vaccine manufactured by Seqirus Pty Ltd. (Seqirus) for the active immunization of persons 5 years of age and older for the prevention of influenza A subtypes and type B viruses contained in the vaccine. The vaccine is a suspension, to be administered via intramuscular injection, and is currently supplied in two presentations – a 0.5 mL pre-filled syringe without a preservative, and a multi-dose vial containing ten 0.5 mL single doses containing thimerosal as a preservative. In this supplement, Seqirus seeks to extend the indication for the Afluria QIV formulation to persons 6 through 59 months which includes a request for approval of a 0.25 mL pediatric dose for persons 6 through 35 months to be supplied as either a single 0.25 mL pre-filled syringe, or as a 0.25 mL dose from the thimerosal-containing multi-dose vial. Afluria QIV is manufactured using the same process as Afluria – a trivalent formulation (TIV) which is also currently approved for use in persons 5 years of age and older. Compared to the TIV formulation, Afluria QIV contains two influenza B virus strains, intended to provide protection against both the B/Yamagata and B/Victoria lineage viruses. The quadrivalent formulation contains 60 mcg of egg-grown viral hemagglutinin (15 mcg each of H1N1, H3N2, B/Victoria and B/Yamagata hemagglutinins). The inclusion of both B lineage viruses is important since infection with B influenza is often severe in children, and it is difficult to predict which B strain will dominate in a given season.

2. BACKGROUND

Afluria TIV, developed by CSL Biotherapies (renamed as bioCSL in 2014), was granted accelerated approval for immunization of persons 18 years of age and older on September 28, 2007 (STN 125254/0). On November 10, 2009, accelerated approval was extended to include children 6 months to 18 years of age in response to the 2009 H1N1 influenza pandemic. This approval was based on safety and immunogenicity data in children 6 months to 9 years of age (it was determined that these data could reasonably be extrapolated to include children 9 to 18 years of age). On December 2, 2011, traditional approval was granted for individuals 18 years of age and older, based on a clinical endpoint efficacy, safety and immunogenicity study in adults 18 to 65 years of age, and a non-inferiority immunogenicity and safety study in adults ≥ 65 years of age (STN 125254/259). This submission also supported traditional approval in children 6 months through 18 years of age based on data from two clinical studies. In July, 2015, bioCSL and the influenza vaccines business of Novartis merged to form Seqirus. Seqirus, along with other manufacturers, developed quadrivalent influenza vaccine formulations to include a second B strain, which gives broader protection against circulating viruses. On August 26, 2016, Afluria QIV was approved in adults 18 years of age and older (STN 125254/565) based on clinical data from a non-inferiority immunogenicity and safety study comparing Afluria QIV to Afluria TIV formulations.

In April 2010, Afluria TIV administered in the Southern Hemisphere, was associated with increased reports of pediatric fever and febrile seizures, predominantly in children less than 5 years of age. Phase 3 pediatric studies also showed higher rates of fever in children less than 9 years of age when compared to a licensed comparator. In response to this, in August 2010, the U.S. Advisory Committee on Immunization Practices (ACIP) recommended that this vaccine not be used in children less than 9 years of age but allowed for its use in children 5 through 8 years of age who were at increased risk of influenza and when no other licensed vaccine was available. A warning was included in the Afluria package insert for the 2010-2011 influenza season, and on July 15, 2011, the use of Afluria TIV was restricted to individuals ≥ 5 years of age.

In 2010, Seqirus began a scientific investigation into the root cause of the increased incidence of fever and febrile seizures. Residual lipids and viral RNA present in the vaccine were found to induce elevated levels of pyrogenic cytokines. (b) (4)

, and resulted in a reduction of these cytokines in vitro. This change was initiated into the manufacturing process, and Seqirus subsequently conducted three clinical studies to assess the impact of this change on vaccine safety.

Study CSLCT-USF-10-69 was a postmarketing safety and tolerability study comparing Afluria TIV to a U.S.-licensed quadrivalent influenza vaccine in children 5 to 9 years of age. Results showed that rates of fever were similar between Afluria and the comparator recipients and therefore supported additional pediatric clinical studies. Study CSLCT-QIV-13-02 was a Phase 3 study designed to support the safety and effectiveness of

Afluria QIV in children 5 through 17 years of age. The primary objective of this study was to demonstrate non-inferiority compared to a licensed quadrivalent influenza vaccine, with a secondary objective to assess safety and tolerability. This study met both endpoints, and the safety profile of Afluria QIV was shown to be similar to that of the comparator. Data from this study was the basis of the August 31, 2017 approval of Afluria QIV in children 5 through 17 years of age, and fulfilled the first of two Postmarketing Requirements associated with the August 26, 2016 approval of Afluria QIV required under the Pediatric Research Equity Act (PREA). On October 31, 2017, Seqirus submitted a supplement to their Biologics License Application containing data from clinical study CSLCT-QIV-15-03, conducted to evaluate the immunogenicity and safety of Afluria QIV in the pediatric population 6 through 59 months of age. This study fulfills the second postmarketing study required under PREA. The data submitted in this study was also included in the Afluria TIV package insert and was used to support the use of the Afluria TIV formulation in individuals 6 through 59 months of age.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

a) Product Quality

The manufacture of monovalent bulk Drug Substance used to formulate Afluria QIV uses the same process as that approved for the manufacture of the Afluria TIV formulation of (STN 125254/0). The formulation and filling process for Afluria QIV was reviewed and approved on August 26, 2016 under STN 125254/565.

The same facilities, equipment, process and process controls used in the manufacture of 0.5 mL pre-filled syringes are applicable to the new 0.25 mL presentation. A process performance qualification (PPQ) study was conducted to verify the filling of the new 0.25 mL presentation and was acceptable. Stability of the 0.25 mL presentation was evaluated up to 12 months and met specifications.

Batch analysis data was provided for the QIV lots used in clinical trial CSLCT-QIV-15-03; all lots used met the approved acceptance criteria. Immunogenicity was based on hemagglutination inhibition (HAI) antibody titer to each strain. Serum samples were analyzed by HAI for the presence of binding antibodies specific to each strain in the study vaccine, and testing was conducted by (b) (4) [REDACTED]. HAI validation reports were reviewed for the four vaccine antigens used in study CSLCT-QIV-15-03: Reports for A/California/7/2009 (H1N1) and B/Brisbane/60/2008 (B Victoria lineage) were reviewed under STN 125254/565; the report for B/Phuket/3073/2013 was reviewed under STN 125254/642 (to extend the indication for Afluria QIV for use in persons 5 years and older); and the report for A/Hong Kong/4801/2014 (H3N2) was reviewed under this STN. All reports were found to be acceptable by the product reviewer.

b) CBER Lot Release

There were no pending lots or issues that would affect approval of this supplement.

c) Facilities review/inspection

Facility information and data provided in the Efficacy Supplement were reviewed by The facility reviewer and found to be sufficient and acceptable. The facilities involved in the manufacture of Afluria QIV TF (Thimerosal-free) and Afluria QIV TC (Thimerosal-containing) are listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Manufacturing Facilities Table for Afluria QIV (Quadrivalent Influenza Vaccine)

Name/Address	FEI Number	DUNS Number	Inspection / Waiver	Justification / Results
<i>Drug Substance</i> Seqirus Pty Ltd 63 Poplar Road Parkville, Victoria, Australia, 3129	30028067 53	74728673 5	Waived	Team Biologics August 8 – 16, 2016 VAI
<i>Drug Product (QIV TF and QIV TC):</i> <i>Formulation, Fill/Finish,</i> <i>Labeling & Packaging,</i> <i>Release Testing</i> CSL Behring GmbH Emil-von-Behring Strasse 76 Marburg, Hesse, Germany, 35041	30030986 80	3265304 74	Waived	Team Biologics May 4 – 17, 2016 VAI
<i>Drug Product (QIV TF):</i> <i>Formulation, Fill/Finish,</i> <i>Labeling & Packaging,</i> <i>Release Testing</i> CSL Behring LLC (b) (4) [REDACTED] [REDACTED]	(b) (4)	(b) (4)	Waived	Team Biologics (b) (4) [REDACTED] VAI

Team Biologics conducted a surveillance inspection of Seqirus Pty Ltd from August 8 – 16, 2016 and FDA form 483 with issues cited was issued. All 483 issues were resolved and the inspection was classified as Voluntary Action Indicated (VAI).

Team Biologics conducted a surveillance inspection of CSL Behring GmbH from May 4 – 17, 2016 and FDA form 483 with issues cited was issued. All 483 issues were resolved and the inspection was classified as Voluntary Action Indicated (VAI).

Team Biologics conducted a surveillance inspection of CSL Behring LLC from (b) (4) [REDACTED]. All FDA Form 483 issues were resolved and the inspection was classified as Voluntary Action Indicated (VAI).

Container Closure

The container closure system for Afluria QIV TF Drug Product is identical to that used for Afluria TIV TF. Accordingly, Afluria QIV TF is dispensed into a 1.25 mL clear (b) (4) glass needle-free syringe and sealed with a chlorobutyl stopper/polystyrene plunger rod assembly. The (b) (4) glass syringe barrel has a Luer-Lok® adapter to permit the attachment of a commercially available needle prior to administration. The Luer-Lok® adapter is sealed with a bromobutyl/isoprene rubber tip cap with a polypropylene shield for protection against damage and contamination. The container closure components are manufactured by Becton, Dickinson and Company.

The container closure system for Afluria QIV TC Drug Product is the same that is used for Afluria QIV TC. Afluria QIV TC is presented in 5.0 mL borosilicate, clear, (b) (4) glass multi-dose vials ((b) (4)). The glass vial is closed with a bromobutyl or chlorobutyl rubber stopper ((b) (4)). The stopper is secured by combination caps ((b) (4)), which consists of an aluminum cap with a concentric hole and an integrated polypropylene plastic disc.

As the container closure systems remain the same as those currently being used for the licensed Afluria TIV and QIV formulations, no container closure integrity testing was performed for Afluria QIV TF and Afluria QIV TC. Container closure integrity had been previously validated by dye leak testing and microbial ingress testing with all acceptance criteria met.

d) Environmental Assessment

The Efficacy Supplement included a request for categorical exclusion from an environmental assessment under 21 CFR 25.31 (c). The FDA concluded that this request is justified as the manufacturing of this product will not significantly alter the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

e) Product Comparability

N/A

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

A reproductive toxicity study of Afluria TIV was conducted in rats using full human doses and was reviewed under STN 125254/124 (Intramuscular reproductive toxicity study of Afluria influenza virus vaccine (IVV) in female rats). All mating and fertility parameters were comparable between control and vaccine groups. No malformations (skeletal and visceral) and no developmental effects caused by and associated with the vaccine were observed. Nonclinical pharmacology/toxicology data were not provided in this supplement because CBER had previously advised Seqirus under IND 15974 that this data would not be needed due to the similarity of Afluria QIV to Afluria TIV.

5. CLINICAL PHARMACOLOGY

The distribution of demographic and baseline characteristics of the 2247 subjects in the Full Analysis Set (FAS) population was similar between treatment groups and age cohorts. Overall, there were more male (51.6%) than female (48.4%) subjects. Most subjects were white (71.0%) and non-Hispanic or Latino (73.1%). Black/African American and Hispanic/Latino subjects comprised 21.5% and 26.4% of the FAS, respectively. American Indian/Alaskan Native (0.3%), Asian (1.1%), Native Hawaiian/Pacific Islander (0.7%) and racial groups identified as “other” (5.3%) comprised the remainder of the FAS. Relative to the U.S. population, blacks/African Americans and Hispanics/Latinos were overrepresented, and Asians were underrepresented.

The mean age (standard deviation) of all subjects in the FAS was 36.6 (14.7) months. 21.7 (8.59) for the 6-35 months age cohort (41.6% of the FAS); and 47.1 (6.94) for the 36-59 months age cohort (58.4% of the FAS). As specified by the protocol, no more than 60% of subjects in the FAS were randomized to either age cohort.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

Study CSLCT-QIV-15-03

Study CSLCT-QIV-15-03 was a prospective, Phase 3, randomized, observer-blinded, comparator-controlled, multicenter study conducted in the U.S. during the Northern Hemisphere (NH) 2016-2017 influenza season in 2250 generally healthy children 6 through 59 months of age. A U.S.-licensed, quadrivalent inactivated influenza vaccine, Fluzone Quadrivalent, manufactured by Sanofi Pasteur, Inc. was used as the active comparator. The study was discussed during a Type B meeting with Seqirus on May 11, 2016, and the final study design was subsequently submitted to IND 15974 (amendment 34).

The Bioresearch Monitoring Branch (BIMO), Division of Inspections and Surveillance, Office of Compliance and Biologics Quality, conducted an inspection of three clinical study sites representing 11% of the vaccinated subjects. Observations from one of the study sites (#8400445) revealed enrollment errors and general non-compliance with the clinical protocol. This inspection was classified as Official Action Indicated (OAI), and compliance action is pending. Because of observations made during the inspection, BIMO recommended excluding the data from site 8400445. There were no problems identified at either of the other two sites inspected. Study site 8400445 represented 3.1% of the Overall Safety Population (OSP) and 2.9% of the Solicited Safety Population (SSP). CBER requested an explanation from Seqirus regarding why the site was not excluded from the final analysis, and a reanalysis of immunogenicity and safety data with the site excluded. Seqirus' reanalysis of the data with site 8400445 excluded showed no impact on the overall conclusion of vaccine safety, and there was no impact on immunogenicity conclusions or overall interpretation of the study data. Seqirus' data

analysis included site 8400445, but appropriately excluded all subjects with protocol deviations according to the statistical analysis plan (and identified prior to database lock). The review of Seqirus' response indicated that they identified problems at the site in a timely manner and aggressively implemented enhanced frequent site monitoring to ensure that all protocol deviations were identified, documented and entered into the clinical database. The justifications provided by Seqirus for inclusion of the site along with the data analysis were reviewed by the Clinical and Statistical reviewers and determined to be acceptable.

The primary objective of CSLCT-QIV-15-03 was to demonstrate that vaccination with Afluria QIV elicits a non-inferior immune response compared to a U.S.-licensed comparator QIV among a pediatric population 6 through 59 months of age. The co-primary endpoints were HAI geometric mean titer (GMT) ratios and seroconversion rate (SCR) differences for each of the four vaccine virus strains at 28 days following final vaccination. The GMT ratio was defined as: GMT Comparator QIV/GMT Afluria QIV.

- SCR was defined as the percentage of subjects with either a pre-vaccination HI titer <1:10 and a post-vaccination HI titer \geq 1:40, or a pre-vaccination HI titer \geq 1:10 and a \geq 4-fold rise in post-vaccination HI titer.
- The SCR difference was defined as: SCR Comparator QIV – SCR Afluria QIV.
- Success criteria for non-inferiority (NI margin): GMT ratio Comparator QIV / Afluria QIV must not exceed 1.5.
- Success criteria for non-inferiority (NI margin): The SCR difference SCR Comparator QIV – SCR Afluria QIV must not exceed 10%.

The above success criteria were specified for each of the four vaccine antigens for a total of 8 co-primary study endpoints.

A total of 2247 subjects were enrolled and stratified into two age cohorts, 6 through 35 months (cohort A) and 36 through 59 months (cohort B), using a quota to ensure that no more than 60% of the total sample size was represented in either age stratum. Following stratification, subjects were randomized 3:1 to receive Afluria QIV or the comparator vaccine in a regimen of one or two vaccinations, depending on vaccination history. All vaccinations were administered intramuscularly (IM) 28 days apart. Children 6 through 35 months received a 0.25 mL dose while children 36 through 59 months received a 0.5 mL dose with each vaccination.

The per protocol population (PPP) was used for the immunogenicity analyses. The PPP was defined as all randomized subjects who received the study vaccine, provided valid pre- and post-vaccination serologies, and did not have any protocol deviations that were medically assessed as potentially impacting immunogenicity results. The PPP included a total of 1940 subjects 6 through 59 months; 1456 received Afluria QIV and 484 received the Comparator QIV vaccine. The results for GMTs, GMT ratios, SCRs and SCR differences together with the 95% confidence intervals (CIs) are shown in Table 1. Afluria QIV elicited immune responses that met pre-specified criteria for non-inferiority relative to the comparator for all four vaccine virus strains.

Table 1: HI Antibody GMTs, SCRs, and Analyses of Non-Inferiority of Afluria QIV Relative to Comparator QIV at 28 Days after Final Vaccination in a Pediatric Population 6 through 59 Months of Age (Per Protocol Population) – CSLCT-QIV-15-03*

Strain	GMT ¹ Afluria QIV (n=1456) ^{6,7}	GMT ¹ Comparator QIV (n=484)	GMT ^{1,2} Ratio (95% CI)	SCR ³ Afluria QIV (n=1456) (95% CI)	SCR ³ Comparator QIV (n=484) (95% CI)	SCR ⁴ Difference (95% CI)	Met NI Criteria ^{2,5}
A/H1N1	353.5 (n=1455) ⁶	281.0 (n=484)	0.79 (0.72, 0.88)	79.1 (76.9, 81.1) (n=1456)	68.8 (64.5, 72.9) (n=484)	-10.3 (-15.4, -5.1)	Yes
A/H3N2	393.0 (n=1454) ^{6,7}	500.5 (n=484)	1.27 (1.15, 1.42)	82.3 (80.2, 84.2) (n=1455) ⁷	84.9 (81.4, 88.0) (n=484)	2.6 (-2.5, 7.8)	Yes
B/Yamagata	23.7 (n=1455) ⁶	26.5 (n=484)	1.12 (1.01, 1.24)	38.9 (36.4, 41.4) (n=1456)	41.9 (37.5, 46.5) (n=484)	3.1 (-2.1, 8.2)	Yes
B/Victoria	54.6 (n=1455) ⁶	52.9 (n=483) ⁸	0.97 (0.86, 1.09)	60.2 (57.6, 62.7) (n=1456)	61.1 (56.6, 65.4) (n=483) ⁸	0.9 (-4.2, 6.1)	Yes

Source: STN 125254/692, Module 5, CSLCT-QIV-15-03 CSR, Tables 11.4-1, 14.2.1.1, and 14.2.2.1

Abbreviations: A/H1N1=A/California/7/2009 (H1N1) pdm09-like virus; A/H3N2=A/Hong Kong/4801/2014 (H3N2)-like virus; B/Yamagata=B/Phuket/3073/2013-like virus; B/Victoria=B/Brisbane/60/2008-like virus; QIV=quadrivalent influenza vaccine; GMT=geometric mean titer; SCR=seroconversion rate; CI=confidence interval, NI=non-inferiority, PPP=Per Protocol Population.

*ClinicalTrials.gov identifier: NCT02914275

¹GMTs adjusted for covariates: vaccine treatment, age stratum, sex, pre-vaccination GMT, influenza vaccination in the prior year, number of doses, and investigator site.

²GMT ratio=Comparator QIV / Afluria QIV.

³SCR defined as percentage of subjects with either a pre-vaccination HI titer <1:10 and post-vaccination HI titer ≥1:40, or a pre-vaccination HI titer ≥1:10 and a 4-fold increase in post-vaccination HI titer.

⁴SCR difference=Comparator QIV SCR minus Afluria QIV SCR.

⁵Non-inferiority criteria for GMT ratio: upper bound (UB) of the two-sided 95% CI on the ratio of Comparator QIV / Afluria QIV must not exceed 1.5. NI criteria for SCR difference: UB of the two-sided 95% CI on the difference between SCR Comparator QIV – Afluria QIV must not exceed 10%.

⁶Subject (b) (6) was excluded from the PPP for the adjusted GMT analysis for the GMT ratio due to unknown previous vaccination history.

⁷Subject (b) (6) had missing A/H3N2 post-vaccination titer.

⁸Subject (b) (6) had missing B/Victoria pre-vaccination titer.

Secondary objectives of study CSLCT-QIV-15-03 were to assess safety and tolerability and to further characterize the immunogenicity of Afluria QIV and a U.S.-licensed Comparator QIV among children 6 through 59 months in two age strata (6 through 35 months and 36 through 59 months) and overall. Analyses of secondary immunogenicity endpoints, pre- and post-vaccination GMTs, the percentage of subjects with post-vaccination (28 days after the final vaccination) HI titers ≥1:40, and SCRs, showed that immune responses were similar between Afluria QIV and Comparator QIV, overall and within each age cohort. In both treatment groups, post-vaccination GMTs were higher against the influenza A strains than the B strains, and higher in subjects 36 through 59 months than 6 through 35 months for all four vaccine strains. A pattern of lower responses to B strains is not unusual for influenza vaccines, and may reflect lower rates of prior wild-type or vaccine exposure to influenza B antigens.

Subpopulation Analyses of Immunogenicity

Subgroup analyses showed a trend towards higher post-vaccination GMTs for A/H1N1 and A/H3N2 strains in black and African American recipients as compared to white recipients. Post-vaccination GMTs for the B strains and SCRs for all four vaccine virus strains were generally similar between the two racial subgroups. Post-vaccination GMTs and SCRs in Hispanic/Latino and non-Hispanic/Latino recipients of Afluria QIV were generally similar for the four vaccine strains in the vaccine. SCRs for the A/H3N2 and B/Victoria antigens trended lower in Hispanic/Latino recipients than in non-Hispanic/Latino recipients. The clinical significance of these observations is unknown and limited by the relatively small sample sizes and descriptive nature of the analyses. The very small sample sizes of other racial groups precluded meaningful analyses.

b) Pediatrics

CBER agreed to the pediatric study plan (PSP) proposed by Seqirus for Afluria QIV under IND 15974 following review by the FDA's Division of Vaccines and Related Products Applications and by the FDA Pediatric Review Committee (PeRC). Studies of Afluria QIV in infants < 6 months of age were waived and studies in children 6 months through 17 years were granted a deferral upon approval of Afluria QIV in persons 18 years and older (STN 125254/565). The waiver in infants < 6 months of age was granted because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients younger than 6 months of age. The deferral of studies in children 6 months through 17 years was granted because the product was ready for approval for use in adults and the pediatric studies in children 6 months through 17 years had not been completed. The two Phase 3 pediatric postmarketing requirements (PMRs) associated with approval of Afluria QIV on August 26, 2016, were to evaluate the safety and immunogenicity of Afluria QIV in children and adolescents 5 years through 17 years and in infants and children 6 months through 4 years. On August 31, 2017, approval of STN 125254/642, an efficacy supplement submitted to extend the indication of Afluria QIV to children and adolescents 5 through 17 years, fulfilled the first PMR.

The assessment for deferred study CSLCT-QIV-15-03 provided in this supplement was presented to the PeRC on April 18, 2018. The PeRC identified no concerns regarding Seqirus' study assessment.

c) Other Special Populations

Information regarding the safety and effectiveness of Afluria QIV in immunocompromised individuals is not sufficient to support specific recommendations in this population. Seqirus agreed to establish a pregnancy registry for Afluria QIV (STN 125254/565) and submitted a pregnancy registry protocol to STN 125254/642. The pregnancy study was scheduled to begin during the NH 2017-2018 influenza season. A separate pregnancy registry was established as a postmarketing commitment for Afluria (TIV formulation) under STN 125254/259 and has been completed. The study results were submitted to the FDA and are currently under review.

7. SAFETY

A secondary objective of the study was to assess the safety and tolerability of Afluria QIV in children 6 through 59 months in two age strata (6 through 35 months and 36 through 59 months). The following endpoints were evaluated by treatment group overall, by age stratum, and (for some analyses) by sex, race, and ethnicity:

- Frequency and severity of solicited local reactions and systemic adverse events (AEs) for seven days following each vaccination (i.e., day of vaccination and 6 subsequent days);
- Frequency of cellulitis-like reaction for at least 28 days after each vaccination (an increase in reports of cellulitis and large injection site swelling was observed during a 2011 review of the worldwide safety database and subsequently included in the *Postmarketing Experience* section of the Afluria package insert [labeling supplement 125254/440]);
- Frequency and severity of unsolicited AEs for at least 28 days after each vaccination (i.e., day of vaccination and 27 subsequent days);
- Frequency of SAEs for 180 days after the final vaccination.

Exploratory Endpoint

- Frequency of antipyretic use in the 7 days after each vaccination, summarized by age and treatment group.

Safety assessments were based on two study populations, the OSP and the SSP. The OSP for study CSLCT-QIV-15-03 included 2232 subjects and was defined as all subjects who received at least one dose or partial dose of study vaccine and for whom any safety data were available after vaccination. The SSP was used to summarize local and systemic reactogenicity data and included all subjects who received at least one dose or partial dose of study vaccine and provided any evaluable data on solicited events. Of the 2163 subjects in the SSP, 1618 received Afluria QIV and 545 received the comparator vaccine. Rates for any and individual solicited local reactions following any vaccination stratified according to age are shown in Table 2.

Table 2: Study CSLCT-QIV-15-03 Rates of Solicited Local Reactions Following Vaccination at any Dose

Solicited local reaction	Afluria Quadrivalent 6-35 months (n = 669)	Comparator vaccine 6-35 months (n = 227)	Afluria Quadrivalent 36-59 months (n = 949)	Comparator vaccine 36-59 months (n = 318)
Any	32.9%	34.4%	44.8%	40.9%
Pain	20.8%	25.6%	35.5%	31.4%
Redness	20.8%	17.6%	22.4%	20.8%
Swelling	6.1%	6.2%	10.1%	12.9%

Source: STN 125254.692, Module 5, CSLCT-QIV-15-03 CSR, Tables 12.2.2-1, 12.2.2-2, 14.3.1.2.2, 14.3.1.2.5, and 14.3.1.2.6.

Of a total of 896 subjects 6 through 35 months (Afluria QIV n=669, Comparator QIV n=227) in the SSP, 32.9% and 34.4%, respectively, reported solicited local reactions,

primarily injection site pain (20.8% and 25.6%, respectively) and redness (20.8% and 17.6%, respectively). Severe local reactions occurred infrequently (0.7% and 2.7% of Afluria QIV and Comparator QIV recipients, respectively). Among 1267 subjects 36 through 59 months in the SSP (Afluria QIV n=949, Comparator QIV n=318), 44.8% and 40.9%, respectively, reported solicited local reactions, primarily injection site pain (35.5% and 31.4%, respectively) and redness (22.4% and 20.8%, respectively). Severe local reactions occurred infrequently (2.7% and 5.7% for Afluria QIV and Comparator QIV recipients, respectively). In both age groups, for subjects who received two vaccinations, rates of local reactions declined following the second vaccination and were mostly mild to moderate in severity.

The rates of solicited systemic AEs following any vaccination stratified according to age are shown in Tables 3 & 4 .

Table 3: Study CSLCT-QIV-15-03 Rates of Solicited Systemic Adverse Events Following any Vaccination in Children 6-35 Months of Age

Solicited systemic AE	Afluria Quadrivalent 6-35 months (n = 669)	Comparator vaccine 6-35 months (n = 227)
Any	48.9%	49.8%
Irritability	32.9%	28.2%
Loss of appetite	20.0%	19.4%
Nausea and/or vomiting	9.4%	11.0%
Diarrhea	24.2%	25.6%
Fever	7.2%	11.9%

Source: STN 125254.692, Module 5, CSLCT-QIV-15-03 CSR, Tables 12.2.2-3, 14.3.1.3.2.1, 14.3.1.3.5.1, and 14.3.1.3.6.1.

Table 4: Study CSLCT-QIV-15-03 Rates of Solicited Systemic Adverse Events Following any Vaccination in Children 36-59 Months of Age

Solicited systemic AE	Afluria Quadrivalent 36-59 months (n = 949)	Comparator vaccine 36-59 months (n = 318)
Any	32.2%	32.1%
Headache	6.2%	5.0%
Myalgia	9.9%	9.4%
Malaise and Fatigue	14.3%	13.2%
Nausea and/or Vomiting	9.2%	6.6%
Diarrhea	12.1%	8.8%
Fever	4.8%	6.0%

Source: STN 125254.692, Module 5, CSLCT-QIV-15-03 CSR, Tables 12.2.2-4, 14.3.1.3.2.1, 14.3.1.3.5.1, and 14.3.1.3.6.1.

Among 896 subjects 6 through 35 months, the most frequently reported solicited systemic symptoms in both the Afluria QIV and comparator groups were irritability, diarrhea, and loss of appetite. Rates were similar between treatment groups. The relative risk (RR) of fever (axillary temperature $\geq 99.5^{\circ}\text{F}$) in Afluria QIV recipients was lower than for recipients of Comparator QIV [RR = 0.60 (95% CI: 0.39, 0.94)], however, the rates of severe Grade 3 fever (axillary temperature $\geq 101.3^{\circ}\text{F}$ or $\geq 38.5^{\circ}\text{C}$) were similar (2.5% vs 2.6%). The proportion of subjects who experienced fever within three days of any vaccination (Day 1 to Day 3) was also lower among recipients of Afluria QIV

than the comparator (3.1% vs 5.3%, respectively). Most events were mild to moderate in severity with a total of 3.1% and 4.0% of Afluria QIV and Comparator QIV recipients, respectively, reporting severe systemic AEs (predominantly fever). The mean onset of solicited systemic AEs was similar between treatment groups. The mean onset of fever was Day 3.8 for Afluria QIV and Day 3.6 for Comparator QIV, with similar mean durations of 1.6 and 1.4 days, respectively. Severe Grade 3 fever (axillary temperature $\geq 101.3^{\circ}\text{F}$ or $\geq 38.5^{\circ}\text{C}$) occurred in 1.7% and 1.3% of Afluria QIV and Comparator QIV recipients, respectively, after the first vaccination, and in 1.7% and 3.4%, respectively, after the second vaccination. No fevers were associated with seizures.

Among 1267 subjects 36 through 59 months, the most frequently reported solicited systemic symptoms in both the Afluria QIV and comparator groups were malaise and fatigue, myalgia and diarrhea. The relative risk of fever in Afluria QIV recipients was slightly lower than for recipients of Comparator QIV but was not statistically significant [RR = 0.81 (95% CI: 0.48, 1.36)]. The rates of severe Grade 3 fever (axillary temperature $\geq 101.3^{\circ}\text{F}$ or $\geq 38.5^{\circ}\text{C}$) were similar between treatment groups (Afluria QIV 1.2% vs Comparator QIV 0.9%). The proportions of subjects who experienced fever within three days of any vaccination (Day 1 to Day 3) were similar between recipients of Afluria QIV and Comparator QIV (2.4% vs 2.2%, respectively). Most events were mild to moderate in severity with a total of 2.0% and 1.6% of Afluria QIV and Comparator QIV recipients, respectively, reporting severe systemic AEs (predominantly fever). The mean onset of fever was Day 3.5 for Afluria QIV and Day 4.3 for Comparator QIV, with similar mean durations of 1.3 and 1.1 days, respectively. No fevers were associated with seizures.

Unsolicited AEs

A total of 707 subjects (31.7% of the OSP) 6 through 59 months reported 1547 unsolicited AEs in the 28 days following vaccination, with similar frequencies between treatment groups overall (Afluria QIV: 32.0%; Comparator QIV: 30.6%) and within age strata. Among subjects 6 through 35 months, 37.6% and 37.8% of Afluria QIV (n=694) and Comparator QIV (n=233) recipients, respectively, reported one or more unsolicited AEs in the 28 days following any vaccination. Among subjects 6 through 35 months who received Afluria QIV, the most common unsolicited AEs (frequency $\geq 1\%$) were: rhinorrhea (11.2%), cough (10.4%), pyrexia (6.3%), upper respiratory tract infection (4.8%), diarrhea (3.7%), otitis media (2.4%), nasal congestion (2.4%), vomiting (2.4%), nasopharyngitis (1.9%), irritability (1.7%), ear infection (1.6%), croup infectious (1.4%), teething (1.3%), rash (1.2%), fatigue (1.0%), and influenza-like illness (1.0%). Among subjects 36 through 59 months, 28.1% of Afluria QIV (n=979) and 25.5% of Comparator QIV (n=326) reported one or more unsolicited AEs in the 28 days following vaccination. The most common unsolicited AEs (frequency $\geq 1\%$) among recipients of Afluria QIV were cough (7.7%), rhinorrhea (4.9%), pyrexia (3.7%), upper respiratory tract infection (2.5%), vomiting (2.1%), nasopharyngitis (1.7%), nasal congestion (1.6%), oropharyngeal pain (1.2%), diarrhea (1.1%), and fatigue (1.1%). In both age strata, most unsolicited AEs were mild to moderate in severity and appeared unrelated to study vaccines. No large imbalances between treatment groups or unusual patterns of specific events were observed.

No cellulitis-like reactions were reported in Afluria QIV recipients during the study.

Serious Adverse Events (SAEs)

The OSP was used for the assessment of SAEs and included 1673 Afluria QIV and 559 Inactivated Influenza Virus, Quadrivalent (IIV4) recipients. In the 180 days following any vaccination, a total of 14 subjects, 11 (0.7%) Afluria QIV and 3 (0.5%) Comparator QIV recipients, reported 15 SAEs. Of the 15 SAEs, 14 occurred in the 6 through 35 months age stratum and 11 occurred more than 28 days after the last vaccination. None of the 15 SAEs appeared related to study vaccines based on a lack of close temporal relationship, lack of biological plausibility, and/or the presence of a more likely pathophysiological mechanism. There were no deaths reported during the study period.

Subpopulation Analyses of Safety

Study CSLCT-QIV-15-03 was not powered for statistical hypothesis testing of rates of adverse events. Because of the small numbers available, the analyses are considered descriptive.

Subpopulation analyses showed similar rates of specific solicited local and systemic adverse events between male and female recipients of Afluria QIV. Overall, black/African American recipients of Afluria QIV had lower rates of specific solicited local injection site and systemic adverse events as compared to whites. The largest differences were observed in the rates of any solicited local reaction, injection site redness, any systemic AE, and irritability. Small sample sizes precluded meaningful analyses of racial subgroups other than blacks/African Americans and whites. Overall rates of solicited local and systemic adverse events were also lower in Hispanic/Latino recipients of Afluria QIV as compared to non-Hispanic/Latinos. Subpopulation analyses also showed trends towards lower rates of unsolicited AEs in females, blacks/African Americans, and Hispanic/Latinos as compared to males, whites, and non-Hispanic/Latinos, respectively. Because the study was not designed to detect statistically significant differences between subpopulations, firm conclusions cannot be drawn from the observed trends.

8. ADVISORY COMMITTEE MEETING

No issues were identified during the review of the supplement that would necessitate presentation before an advisory committee.

9. OTHER RELEVANT REGULATORY ISSUES

On July 18, 2018, CBER's Bioresearch Monitoring Branch identified an issue with clinical study site 8400445, raising questions about the quality and integrity of data from this site. Seqirus informed CBER that subject data from this site were collected in accordance with the study protocol and analyzed in accordance with the Statistical Analysis Plan (SAP). All subjects with protocol deviations identified during the inspection were identified by Seqirus prior to database lock and were excluded from the

immunogenicity analysis. At CBER's request, a reanalysis of data excluding study site 8400445 was carried out. It was determined that there was no impact on the overall interpretation of the study data, with all eight co-primary endpoints still meeting the criteria for non-inferiority. Taking these two factors into consideration, there appears to be no impact on the overall interpretation of the study data and conclusions, and it was determined that inclusion of the site in the final analysis was acceptable.

10. LABELING

The Afluria QIV package insert was revised to include safety and immunogenicity data for children 6 through 59 months of age from study CSLCT-QIV-15-03. The Afluria TIV package insert was also revised to include safety and immunogenicity data for children 6 through 59 months of age from study CSLCT-QIV-15-03; data from studies of Afluria TIV were retained for children and adolescents 5 through 17 years of age and for adults. Section 8.4 (Pediatric Use) was updated for both the Afluria TIV and Afluria QIV package inserts to remove a reference to increased rates of fever and febrile seizures predominantly in children less than 5 years of age in the 2010 Southern Hemisphere season.

The Advertising and Promotional Labeling Branch (APLB) found the prescribing information and carton/container labels for Afluria QIV to be acceptable from a promotional and comprehension perspective.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The Review Committee recommends approval of Afluria Quadrivalent in children 6 through 59 months based on data demonstrating that Afluria Quadrivalent elicited a non-inferior immune response in this population as compared to a U.S.-licensed Comparator, and on the vaccine's acceptable safety profile. Rates of vaccine-related febrile seizures (zero), febrile events, and severe reactogenicity following vaccination were acceptable and will continue to be monitored through routine postmarketing surveillance.

b) Risk/ Benefit Assessment

Afluria TIV has demonstrated clinical efficacy in adults 18 through 49 years (STN 125254/259). Afluria QIV demonstrated non-inferior immunogenicity to a U.S.-licensed Comparator QIV in a pediatric population 6 through 59 months, suggesting that it is likely to confer protection against influenza similar to Afluria TIV for strains common to both vaccines, and additional protection against the alternate B strain as compared to the TIV formulation. Lower immune responses elicited against the influenza B vaccine antigens as compared to influenza A were observed for both Afluria QIV and the comparator, and have also been observed in studies of other inactivated

influenza vaccines. Because Afluria QIV is manufactured by the same process as Afluria TIV and has demonstrated non-inferior immunogenicity, a clinical endpoint study to confirm clinical benefit is not necessary.

The safety profile of Afluria QIV was comparable to a U.S.-licensed QIV and was clinically acceptable. No vaccine-related febrile seizures were reported in the study and, importantly, no seizures occurred in the seven days post-vaccinations. Rates of fever among subjects 6 through 59 months, in the 7 days following vaccination with Afluria QIV were notably lower than historical rates for Afluria TIV and similar to Comparator QIV. Consistent with conclusions from Seqirus' scientific investigation of the root cause of febrile seizures and other febrile events associated with the Southern Hemisphere 2010 formulation of Afluria, the higher concentration (1.5%) of TDOC used to split each of the four Afluria QIV vaccine virus strains used in study CSLCT-QIV-15-03 appears associated with less pyrogenicity. Given the effectiveness against a potentially serious and life-threatening disease, it is reasonable to conclude that the potential benefits of Afluria QIV outweigh potential risks in children and adolescents 6 through 59 months. Routine postmarketing surveillance is sufficient and will help clarify whether the lower rates of fever observed in CSLCT-QIV-15-03 are generalizable to a broader population 6 through 59 months or to future vaccine formulations containing different antigens.

c) Recommendation for Postmarketing Activities

No new postmarketing activities were deemed necessary. This study fulfills the second of two postmarketing studies required by the Pediatric Research Equity Act (PREA).