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BLA Clinical Review Memorandum

Application Type	Efficacy Supplement to extend the indication to children 6-59 months.
STN	125254.692
CBER Received Date	October 31, 2017
PDUFA Goal Date	December 1, 2018
Division / Office	DVRPA/OVRR
Priority Review	No
Reviewer Name	Cynthia Nolletti, MD
Review Completion Date / Stamped Date	August 21, 2018 September 7, 2018
Supervisory Concurrence	Meghan Ferris, MD, MPH Team Leader CRB2 Andrea Hulse, MD Chief, CRB2
Applicant	Seqirus Pty Ltd
Established Name	Quadrivalent Influenza Vaccine
Trade Name	Afluria Quadrivalent
Pharmacologic Class	Vaccine
Formulations, including Adjuvants, etc.	Each 0.5mL dose contains 15µg hemagglutinin (HA), total 60µg, from four influenza types and subtypes: A/H1N1, A/H3N2, B/Yamagata, and B/Victoria. The multidose vial also contains thimerosal (24.5 mcg mercury per 0.5mL dose).
Dosage Form and Route of Administration	Sterile suspension for intramuscular (IM) injection supplied in single dose 0.25 mL and 0.5 mL pre-filled syringes, and 5 mL multidose vials (ten 0.5 mL doses).
Dosing Regimen	One 0.5mL dose IM by needle-syringe (persons ≥9 years) or PharmaJet Stratis Needle-Free Injection System (adults 18 through 64 years).

	One or two doses (based on prior vaccination history) IM ≥1 month apart by needle-syringe: • 0.25 mL in persons 6-35 months • 0.5 mL in persons 36 months through 8 years
Indication and Intended Population	Active immunization against influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. Persons ≥6 months.
Orphan Designated	No

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GLOSSARY

ACIP	Advisory Committee for Immunization Practices
AE	adverse event
AESI	adverse event of special interest
BLA	biologics license application
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	complete study report
DSMB	data safety monitoring board
EP	Evaluable Population
ES	Executive Summary
FAS	full analysis set
GMT	geometric mean titer
HA	hemagglutinin
HI	hemagglutination inhibition
IIV	inactivated influenza vaccine
IIV3	trivalent inactivated influenza vaccine
IIV4	quadrivalent inactivated influenza vaccine
IM	intramuscular
LAIV	live attenuated influenza vaccine
LB	lower bound
MAE	medically attended event
mcg	microgram
MedDRA	Medical Dictionary for Regulatory Activities
NA	neuraminidase
NH	northern hemisphere
NI	non-inferiority
OBE	Office of Biostatistics and Epidemiology
OBE/DE	Office of Biostatistics and Epidemiology/Division of Epidemiology
OSP	Overall Safety Population
PeRC	Pediatric Review Committee (CDER)
PI	package insert
PMC	postmarketing commitment
PMR	postmarketing requirement
PPP	Per Protocol Population
PREA	Pediatric Research Equity Act
PSP	Pediatric Study Plan
PVP	Pharmacovigilance Plan
PT	Preferred Term
QIV	quadrivalent influenza vaccine
REMS	risk evaluation and mitigation strategy
RIV	recombinant influenza vaccine
RNA	ribonucleic acid

RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SCR	seroconversion rate
SH	southern hemisphere
SOC	system organ class
SSP	Solicited Safety Population
TDOC	sodium taurodeoxycholate
TEAE	treatment emergent adverse event
TIV	trivalent influenza vaccine
VAERS	Vaccine Adverse Event Reporting System
VAMPSS	Vaccines and Medications in Pregnancy Surveillance System
VRBPAC	Vaccine and Related Biologics Products Advisory Committee
UB	upper bound

1. Executive Summary

In the current efficacy supplement, Seqirus submitted data from a single study, CSLCT-QIV-15-03, to support the safety and effectiveness of Afluria QIV in a pediatric population 6 through 59 months and extend the usage to this population. The sponsor submitted a Major Amendment (STN 125254/692.14) to this supplement on August 2, 2018 in response to an FDA request for information and additional analyses relating to issues raised by a Bioresearch Monitoring (BIMO) inspection regarding study conduct at one clinical study site. Therefore, on August 7, 2018, the Action Due Date was extended from September 1, 2018 to December 1, 2018.

The BIMO Establishment Inspection Report (EIR) for study site #8400445, which included 69 vaccinated subjects (Afluria QIV n=54; Comparator QIV n=15), noted numerous protocol deviations (discovered by site monitors and reported to the sponsor), incomplete and/or inaccurate source documents, and lack of contemporaneousness in documentation, raising questions about the quality and integrity of the data. However, the BIMO inspector also noted that all reports to the sponsor and data submitted to the Contract Research Organization (CRO) and the sponsor via the eCRF, electronic data capture (EDC) system, and site monitor visits, appeared on time and complete. The EIR was reviewed in detail as were the data for subjects at this site. All protocol deviations noted in the EIR were reported in the Complete Study Report (CSR) tables and listings, Statistical Analysis Plan (SAP) listings, and electronic datasets.

To address concerns regarding the quality and integrity of the data, the clinical review team requested information from the sponsor, including a rationale for not excluding the site from the final study analyses and not highlighting problems noted at the site in the body of the CSR. The sponsor was also asked to provide repeat demographic, immunogenicity and safety analyses excluding site #8400445. The sponsor's response to our information request (please see STN 125254/692 Amendments 13 and 14), indicated that the sponsor 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. Subjects appeared to have been appropriately excluded from the immunogenicity populations according to the protocol and Statistical Analysis Plan (SAP). Of 69 vaccinated subjects, 41 (59.4%) were included in the Per Protocol Population (PPP) as compared to 86.3% of

subjects included the PPP for the entire study. The sponsor also noted that solicited and unsolicited adverse events were entered into electronic diaries by parents and/or guardians in real time, independent of the site investigators, and that the sponsor monitored electronic diary completion rates on a weekly basis. The electronic diary completion rate for the site was 80% deemed high and comparable to 87% for the entire study population. Overall, 62 of 69 vaccinated subjects (89.9%) provided safety information and were included in the Safety Population (SP).

The sponsor's additional analyses excluding site #8400445 were reviewed in detail. For the primary immunogenicity analysis, differences between results reported in the CSR (all study sites) and repeat analyses excluding site #8400445 were no more than 0.02 for upper bounds (UB) on the 95% confidence intervals (CI) for geometric mean titer (GMT) ratios, and no more than 0.9% for UBs on the 95% CIs for seroconversion rate (SCR) differences. The primary endpoint would have been met had site #8400445 been excluded. Regarding safety data, additional analyses demonstrated that exclusion of site #8400445 yielded minimal differences (< 1%) in the rates of any solicited or unsolicited AE overall, specific event rates, and rates according to severity grade or relatedness. For most events, including solicited local and systemic AEs and fever, rates of specific events in the repeat analyses excluding site #8400445 were identical or differed only by 0.1%-0.2% as compared to the rates for the entire study population reported in the CSR. Thus, the clinical review team concluded that analyses excluding site #8400445 had no clinically significant impact on the overall interpretation of the study data.

The clinical reviewers acknowledged BIMO's decision to recommend exclusion of site #8400445. However, considering the sponsor's enhanced site monitoring ensuring that data were entered into the clinical database, appropriate exclusion of major protocol deviations, and minimal differences between final analyses reported in the CSR and additional analyses excluding site #8400445, the clinical review team agreed with the sponsor's decision to allow site #8400445 to continue in the study and to include data from the study in the final analyses and Package Insert. The statistical reviewer confirmed the accuracy of the sponsor's additional analyses and agreed with this approach.

Afluria Quadrivalent (also referred to as "Afluria QIV" or "Seqirus QIV" in this review) is an inactivated, split virion quadrivalent influenza vaccine (QIV) indicated for active immunization against influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine, and was initially approved for use in adults 18 years and older on August 26, 2016. Afluria QIV is manufactured by Seqirus Pty, Ltd (also referred to as "the Applicant" in this review, and previously known as BioCSL Pty, Ltd). Afluria QIV is manufactured in eggs by the same process as Afluria Influenza Vaccine, a trivalent formulation (TIV) initially approved on September 28, 2007 and currently licensed for use in persons 5 years and older. Unlike the trivalent formulation, Afluria QIV contains two B virus strains, one from each of the two phylogenetic lineages. Quadrivalent influenza vaccines mitigate the potential for antigenic mismatch and poor efficacy associated with an incorrect prediction of which B lineage virus will predominate in any given season. The dosing regimen of Afluria QIV in adults is 60 mcg [15 mcg hemagglutinin (HA) per antigen] administered intramuscularly (IM).

Afluria TIV was granted accelerated approval in children and adolescents 6 months through 17 years in the U.S. on November 10, 2009 in response to the 2009 H1N1

influenza pandemic. In April 2010, administration of the Southern Hemisphere (SH) 2010 formulation of Seqirus TIV was associated with increased postmarketing reports of febrile seizures and other febrile adverse events, predominantly in children <5 years. Concurrent with these reports, ongoing Phase 3 pediatric studies to support traditional approval of Afluria TIV also showed higher rates of fever in children <9 years as compared to an active U.S.-licensed comparator. Therefore, on July 15, 2011, FDA restricted the indication for Afluria TIV to children and adolescents ≥5 years.

Following a scientific investigation into the root cause of the SH 2010 febrile seizures, Seqirus found that residual lipids and RNA fragments present in the final vaccine formulation induced production of pro-inflammatory cytokines and a pyrogenic response. The investigation also showed that (b) (4) induction of pro-inflammatory cytokines in vitro, and Seqirus hypothesized that (b) (4) might reduce the pyrogenicity of Afluria in children. Seqirus has since modified the formulation of Afluria QIV to (b) (4), and used this formulation in a study that supported approval of Afluria QIV in the pediatric population of children and adolescents 5 through 17 years on August 31, 2017 (STN 125254/642).

In the current efficacy supplement, Seqirus submitted data from a single study, CSLCT-QIV-15-03, to support the safety and effectiveness of Afluria QIV in a pediatric population 6 through 59 months. 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, to evaluate the safety and immunogenicity of Afluria QIV in 2250 generally healthy children 6 through 59 months. Subjects were stratified into two age cohorts (6 through 35 and 36 through 59 months), and randomized 3:1 to receive Afluria QIV or a U.S.-licensed 2016-2017 comparator quadrivalent inactivated influenza vaccine (Fluzone Quadrivalent, Sanofi Pasteur, Inc., referred to as "Comparator QIV" in this review) in a regimen of one or two vaccinations, depending on vaccination history, administered intramuscularly (IM) 28 days apart. Children 6 through 35 months received a 0.25 mL half dose while children 36 through 59 months received a full dose of 0.5 mL with each vaccination. Immune responses to the study vaccines were measured by hemagglutination inhibition (HI) antibody titers to each of the influenza virus antigens contained in the study vaccines, collected prior to vaccination on Day 1 and again 28 days after the final vaccination. Safety was evaluated by active solicitation of local and systemic symptoms and temperature for 7 days following each vaccination, and passive recording of unsolicited adverse events (AEs) and concomitant medications for 28 days following each vaccination, using an electronic diary. Cellulitis-like reactions and influenza-like illness (ILI) were monitored for 28 days following each vaccination. Serious adverse events (SAEs) and adverse events of special interest (AESIs), defined as medically significant events associated with the pharmacologic class of influenza vaccines, were monitored for the duration of the trial (180 days after the last vaccination in each subject).

The primary objective of the study was to demonstrate that vaccination with Afluria QIV elicits an immune response that is not inferior to that of a U.S.-licensed comparator QIV containing the same virus strains as Afluria QIV, in a pediatric population 6 through 59 months. Secondary objectives were to assess safety and tolerability and to further characterize the immunogenicity of Afluria QIV and a U.S.-licensed QIV among children

6 through 59 months in two age strata (6 through 35 months and 36 through 59 months) and overall.

CSLCT-QIV-15-03 pre-specified eight co-primary endpoints of post-vaccination (28 days after the final vaccination) HI geometric mean titer (GMT) ratios and seroconversion rate (SCR) differences for each of four vaccine virus strains for the immunogenicity population comprised of both age groups (6-59 months). Seroconversion was defined as achieving a 4-fold increase in post-immunization HI titer from a baseline of ≥ 1:10, or a post-immunization HI titer of ≥1:40 if the baseline was < 1:10. The non-inferiority (NI) endpoints and success criteria used in this study are commonly used in the evaluation of effectiveness of influenza vaccines. Non-inferior immunogenicity of Afluria QIV as compared to Comparator QIV was assessed in accordance with FDA guidance[35], and was demonstrated if, for each of the four vaccine virus strains:

- The upper bound (UB) of the two-sided 95% confidence interval (CI) for the GMT ratio (GMT Comparator QIV / GMT Afluria QIV) was ≤ 1.5, *AND*
- The UB of the two-sided 95% CI for the SCR difference (SCR Comparator QIV – SCR Afluria QIV) was ≤ 10%.

Serum HI antibodies to each vaccine virus strain, measured prior to vaccination on Day 1 and 28 days after the final vaccination, were used to calculate secondary endpoints for subjects in each age stratum and overall. Secondary endpoints included GMTs, SCRs, and the proportion of subjects with HI titers ≥ 1:40 (% HI ≥ 1:40) at post-vaccination Day 28 for all four antigens in each treatment group. Secondary endpoints were also calculated according to sex, race and ethnicity.

Summary of Immunogenicity

The Per Protocol Population (PPP) was used for the primary and secondary immunogenicity analyses, and was defined as all randomized subjects who received study vaccine, provided valid pre- and post-vaccination serologies, and did not have any protocol deviations that were medically assessed as potentially affecting immunogenicity results. The PPP included a total of 1940 subjects 6 through 59 months, of whom 1456 received Afluria QIV and 484 received Comparator QIV. Table 1 presents results of the eight co-primary endpoints and non-inferiority analyses of post-vaccination HI GMTs, GMT ratios, SCRs, and SCR differences for each of four antigens contained in the study vaccines. 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 (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?[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

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?[5]
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
[1]GMTs adjusted for covariates: vaccine treatment, age stratum, sex, pre-vaccination GMT, influenza vaccination in the prior year, number of doses, and investigator site.
[2]GMT ratio=Comparator QIV / Afluria QIV.
[3]SCR 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.
[4]SCR difference=Comparator QIV SCR minus Afluria QIV SCR.
[5]Non-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%.
[6]Subject (b) (6) was excluded from the PPP for the adjusted GMT analysis for the GMT ratio due to unknown previous vaccination history.
[7]Subject (b) (6) had missing A/H3N2 post-vaccination titer.
[8]Subject (b) (6) had missing B/Victoria pre-vaccination titer.

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 36-59 months than 6-35 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.

Summary of Safety

The Overall Safety Population (OSP) was used to summarize all safety data, and included all randomized subjects 6 through 59 months who received at least one dose or partial dose of study vaccine and provided any evaluable safety follow-up data. The OSP was comprised of 2,232 subjects, including 1673 and 559 vaccinated with Afluria QIV or Comparator QIV, respectively. No subjects in the OSP died during the 6 months following vaccination, and no discontinuations (Afluria QIV 7.5%, Comparator QIV 7.1%) were due to AEs.

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 a total 15 SAEs, 14 occurred in the 6-35 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.

The Solicited Safety Population (SSP) was used to summarize local and systemic reactogenicity data, and was comprised of all randomized subjects who received at least one dose or partial dose of study vaccine and provided any evaluable data on solicited

adverse events. 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 36-59 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 mean onset of all local reactions occurred between Day 1 and Day 2, and the mean duration was less than 2 days. No cellulitis-like reactions occurred in Afluria QIV recipients during the study.

Among Afluria QIV and Comparator QIV recipients 6 through 35 months, 48.9% and 49.8%, respectively, reported solicited systemic AEs. The most frequently reported symptoms in both groups, respectively, were irritability (32.9% vs 28.2%), diarrhea (24.4% vs 25.6%), and loss of appetite (20.0% vs 19.4%). Fever (axillary temperature ≥99.5°F) occurred in fewer recipients of Afluria QIV than Comparator QIV [7.2% vs 11.9%, respectively, RR = 0.60 (95% CI: 0.39, 0.94)], however, the rates of severe Grade 3 fever (axillary temperature ≥101.3°F or ≥38.5°C) were similar (2.5% vs 2.6%). The proportion of subjects who reported 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). Severe systemic symptoms were relatively infrequent, occurring in 3.1% and 4.0% of Afluria QIV and Comparator QIV recipients, respectively, (predominantly fever as noted).

Among Afluria QIV and Comparator QIV recipients 36 through 59 months, 32.2% and 32.1%, respectively, reported solicited systemic AEs. The most frequently reported symptoms in both groups, respectively, were malaise and fatigue (14.3% vs 13.2%), myalgia (9.9% vs 9.4%), and diarrhea (12.1% vs 8.8%). Imbalances between treatment groups were small. Fever (axillary temperature ≥99.5°F) occurred in similar proportions of Afluria QIV and Comparator QIV recipients [Afluria QIV 4.8% vs Comparator QIV 6.0%, RR = 0.81 (95% CI: 0.48, 1.36)] as did severe Grade 3 fever (axillary temperature ≥101.3°F or ≥38.5°C) (Afluria QIV 1.2% vs Comparator QIV 0.9%). The proportion of subjects who reported fever within three days of any vaccination (Day 1 to Day 3) was also similar between treatment groups (Afluria QIV 2.4%, Comparator QIV 2.2%). Severe systemic symptoms, overall, were infrequent, occurring in 2.0% and 1.6% of Afluria QIV and Comparator QIV recipients, respectively, (predominantly fever as noted).

In both age cohorts, the mean onset and duration of systemic symptoms were similar between treatment groups, and, among Afluria QIV recipients who received two vaccinations, the rates of solicited systemic AEs were lower following the second vaccination. No febrile seizures occurred in either age or treatment group in the 7 days following any vaccination during the study.

A total of 707 subjects (31.7% of the OSP) 6 through 59 months reported 1,547 unsolicited AEs in the 28 days following vaccination, with similar frequencies between treatment groups overall (Afluria QIV 32.0%, Comparator 30.6%) and within age strata. More unsolicited AEs were reported by subjects 6-35 months as compared to 36-59

months overall (37.6% vs 27.4%). The most common AEs were events generally anticipated in the age groups evaluated. 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. Two unrelated febrile seizures occurred in Afluria QIV recipients (6-35 months age group) at 43 and 104 days post-vaccination.

Overall, rates of solicited local and systemic AEs in both age strata (6-59 months), including fever and severe AEs, in recipients of Afluria QIV were acceptable without unusual patterns or safety concerns.

PREA Considerations

Submission of STN 125254/565, the efficacy supplement supporting initial approval of Afluria QIV in adults, triggered the Pediatric Research Equity Act (PREA) because it contained a new active ingredient (a second influenza type B virus antigen). The Pediatric Study Plan (PSP), approved by CBER and the Pediatric Research Committee (PeRC), included a partial waiver in children from birth to <6 months (because Afluria QIV does not represent meaningful therapeutic benefit over initiating vaccination at 6 months of age and is not likely to be used in a substantial number of infants younger than 6 months) and deferral of studies in two pediatric age groups because the product was ready for approval for use in adults and pediatric studies 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.

Submission of STN 125254/692 required a PeRC review because the supplement contained an assessment associated with a PREA PMR. On April 18, 2018, the PeRC concurred with the review team's assessment that data from CSLCT-QIV-15-03 support licensure of Afluria QIV in children 6 months through 4 years. With approval of this efficacy supplement, Seqirus will fulfill the second PMR.

Pharmacovigilance Plan (PVP) – PMCs, PMRs

The Applicant will continue routine monitoring of severe reactogenicity, other identified risks (hypersensitivity and anaphylaxis), and potential risks associated with influenza vaccination (encephalomyelitis, seizures/convulsions, Guillain-Barre syndrome, transverse myelitis, optic neuritis, Bell's palsy, serum sickness, and large/extensive injection site swelling and cellulitis-like reactions). At the time the clinical review was completed, OBE/DE had not recommended a PMR designed specifically to evaluate safety as a primary endpoint, a risk evaluation and mitigation strategy (REMS), or a Black Box warning for administration of Afluria QIV, but will continue to monitor febrile reactions and injection site swelling through postmarketing surveillance. In accordance with the postmarketing commitment (PMC) associated with approval of Afluria QIV in adults (STN 125254/565), exposure, safety, and outcomes in pregnancy will be assessed by a pregnancy registry, a prospective observational study of pregnant women exposed to Afluria QIV. Please see the OBE/DE review for a full discussion of the PVP, PREA Considerations of this section, and Sections 9.1.1 and 9.1.3 for further discussion of the pregnancy PMC and pediatric PMRs.

Recommendation based on Risk Benefit
From the clinical perspective, the safety and immunogenicity data from CSLCT-QIV-15-03 support a recommendation for traditional approval of Afluria QIV in the pediatric population 6 years through 59 months of age.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

This efficacy supplement consisted of one clinical trial comparing the safety and immunogenicity of Afluria QIV to a U.S.-licensed comparator. The distribution of demographic and baseline characteristics of the 2247 subjects in the full analysis set (FAS) population (all subjects whose parents/guardians provided informed consent and were randomized to treatment) 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 (13.2%) and Hispanics/Latinos (17.7%) were overrepresented, and Asians (5.5%) were underrepresented.

The mean age (SD) 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.

Subpopulation Analyses of Immunogenicity
Subpopulation analyses conducted by sex, race and ethnicity were pre-specified secondary descriptive analyses, not powered for statistical hypothesis testing. Subgroup analyses showed that post-vaccination (28 days after the final vaccination) GMTs, % HI ≥1:40, and SCRs were similar between sexes in each treatment group. Subgroup analyses of secondary endpoints conducted for white and black race and Hispanic/Latino and non-Hispanic/Latino ethnicity followed patterns observed in the overall Per Protocol Population, and were similar between treatment groups. Post-vaccination GMTs in black and African American recipients of Afluria QIV showed a trend towards higher GMTs (non-overlapping 95% CIs) as compared to whites for the A/H1N1 and A/H3N2 strains included in the vaccines. However, post-vaccination GMTs for the B strains and post-vaccination % HI ≥1:40 and SCRs for all four vaccine virus strains were generally similar between the two racial subgroups. Post-vaccination GMTs, post-vaccination % HI ≥1:40, and SCRs in Hispanic/Latino and non-Hispanic/Latino recipients of Afluria QIV were generally similar for the four vaccine strains included in the vaccines. SCRs for the A/H3N2 and B/Victoria antigens trended lower in Hispanic/Latino recipients than in non-Hispanic/Latino recipients of Afluria QIV. 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.

Subpopulation Analyses of Safety – Solicited Adverse Events
Rates of deaths and SAEs in CSLCT-QIV-15-03 were too low to perform meaningful subpopulation analyses.

Sex
Among the pediatric population 6-59 months, 38.4% and 41.5% of male and female recipients of Afluria QIV, respectively, experienced solicited local injection site reactions, and 39.1% and 39.2%, respectively, experienced solicited systemic AEs. Subpopulation analyses showed similar rates of specific solicited local and systemic adverse events between male and female recipients of Afluria QIV.

Race
Among the pediatric population 6-59 months, 30.0% and 43.0% of black/African American and white recipients of Afluria QIV, respectively, experienced solicited local injection site reactions. 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 (30.0% vs 43.0%), injection site redness (11.0% vs 25.4%), any systemic AE (28.1% vs 42.8%), and irritability (18.6% vs 36.1%). Small sample sizes precluded meaningful analyses of racial subgroups other than blacks/African Americans and whites.

Ethnicity
Among the pediatric population 6-59 months, 36.1% and 41.2% of Hispanic/Latino and non-Hispanic/Latino recipients of Afluria QIV, respectively, experienced solicited local injection site reactions, and 32.3% vs 41.4%, respectively, experienced solicited systemic AEs. The largest difference observed between Hispanic/Latinos and non-Hispanic/Latinos was in the rate of diarrhea (10.4% vs 19.5%, respectively).

Subpopulation Analyses of Safety – Unsolicited Adverse Events
Sex
Overall, males in both treatment groups (Afluria QIV 34.3%, Comparator QIV 35.9%) experienced higher rates of unsolicited AEs in the 28 days following vaccination than females (Afluria QIV 29.7%, Comparator QIV 24.6%), but differences in specific events were small and not clinically significant. Among Afluria QIV recipients, differences between males and females in the rates of specific events as categorized by SOC were <3%, and as categorized by PT <2%.

Race
Sub-analyses of racial groups revealed lower rates of unsolicited AEs in blacks/African Americans as compared to whites. Overall rates of unsolicited AEs in black/African Americans vs white Afluria QIV recipients were 19.0% and 35.9%, respectively, and, among Comparator QIV recipients, 23.1% and 33.2%, respectively. Small sample sizes precluded meaningful sub-analyses of unsolicited AEs in other racial groups.

Ethnicity
The overall rates of unsolicited AEs in both treatment groups were lower in Hispanic/Latinos as compared to non-Hispanic/Latinos (Afluria QIV 28.4% vs 33.4%; Comparator QIV 22.8% vs 33.9%).

Reviewer comment: Overall, subpopulation analyses of Afluria QIV recipients showed no large imbalances in rates of solicited AEs by sex and trends towards lower rates of solicited local and systemic AEs in blacks/African Americans and Hispanic/Latinos as compared to whites and non-Hispanic/Latinos, respectively. 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. The reasons for these trends are unknown. Because the study was not designed to demonstrate differences between subpopulations using inferential statistics, we cannot draw firm conclusions from the observed trends.

2. Clinical and Regulatory Background

On September 28, 2007, Afluria (Seqirus' trivalent split virion inactivated influenza vaccine) was approved for active immunization against influenza disease caused by influenza A subtype viruses and the type B virus contained in the vaccine in adults 18 years and older. The dosing regimen of the trivalent formulation in adults is 45 µg [15 µg of HA antigen per virus strain] administered IM. Afluria TIV was granted accelerated approval in children and adolescents 6 months through 17 years in the U.S. on November 10, 2009 in response to the 2009 H1N1 influenza pandemic. In April 2010, administration of the SH 2010 formulation of Seqirus TIV was associated with increased postmarketing reports of febrile seizures and other febrile adverse events, predominantly in children <5 years. Concurrent with these reports, ongoing Phase 3 pediatric studies to support traditional approval of Afluria TIV also showed higher rates of fever in children <9 years as compared to an active U.S.-licensed comparator. Therefore, on July 15, 2011, FDA restricted the indication for Afluria TIV to children and adolescents ≥5 years. Please see Sections 2.4 and 2.5 of this review for details of this regulatory history and the scientific investigation into the root cause of the SH 2010 febrile seizures. Ultimately, (b) (4) used in the manufacturing process resulted in a less pyrogenic formulation, confirmed in subsequent pediatric studies. On August 26, 2016, FDA approved Afluria Quadrivalent, a new formulation containing A/H1N1, A/H3N2, and two type B virus strains, representing both B virus genetic lineages (Yamagata and Victoria) (dosage 60 µg), for use in adults ≥18 years. On August 31, 2017, FDA extended the indication for Afluria QIV to persons 5 through 17 years. In this efficacy supplement, the Applicant has submitted safety and immunogenicity data to support extension of the indication for Afluria QIV and Afluria (trivalent formulation) to persons 6 months through 5 years.

2.1 Disease or Health-Related Condition(s) Studied

Influenza is an important infectious cause of death in the United States and throughout the world, with influenza-associated respiratory and circulatory mortality rates ranging from 3,349 to 48,614 in the U.S. from 1976 to 2007 (average annual mortality of 23,607) and 250,000 to 500,000 deaths worldwide each year. It is responsible for more deaths in the U.S. than all other vaccine-preventable diseases combined. In seasons when influenza A/H3N2 predominates, mortality has been 2.7 times higher than when other strains (A/H1N1 or B) have predominated. A Centers for Disease Control and Prevention (CDC) study covering the period 1990-1999, during which A/H3N2 predominated in the U.S., estimated an annual average mortality of 36,155. During seasonal influenza epidemics in the U.S. from 1979-2001, the CDC estimated that influenza-associated hospitalizations ranged from 55,000 to 431,000 per season. More recently, the CDC estimated that influenza resulted in 9.2 million to 60.8 million illnesses, 114,018 to 633,001 hospitalizations, 18,476 to 96,667 intensive care unit admissions, and 4,866 to 27,810 deaths annually since 2010. Complications, hospitalizations and deaths from seasonal influenza disproportionately affect persons ≥ 65 years, children < 5 years, especially those < 2 years, and persons of any age with certain underlying cardiac, respiratory, metabolic, or immune compromising medical conditions. Estimates

of influenza-associated hospitalizations among children <1 year and 1-4 years of age during 1993-2008 were 151.0 and 38.8 per 100,000, respectively. Pediatric mortality due to influenza is <1 per 100,000 per person years. The absolute numbers of pediatric deaths since 2004 have ranged from 37 to 171, annually, with a higher number of 358 deaths during the 2009 H1N1 pandemic. [6,10,11,12,13,14,16,17,23,24,29,33,35,79]

Influenza is caused by RNA viruses of the family Orthomyxoviridae. Two types, influenza A and influenza B, cause the vast majority of human disease. Influenza A is further categorized into subtypes based on two surface antigens, hemagglutinin (HA) and neuraminidase (NA), which comprise the viral glycoprotein coat. There are multiple subtypes of influenza A based on combinations of 18 variants of HA and 11 variants of NA, but only subtypes H1N1, H2N2, and H3N2 appear to circulate widely in humans. Influenza A is also isolated from non-human species including birds, horses, and swine. In contrast to influenza A, influenza B is comprised of single HA and NA subtypes, and occurs almost exclusively in humans. Antibodies to the immunodominant influenza HA globular head epitopes are subtype and strain-specific, and confer protection against future infection with identical strains, but not against another type or subtype. Historically, the A/H3N2 strain has been associated with a higher mortality rate as compared to the A/H1N1 or B strains, although the B strain is known to cause serious disease in children. [12,13,36,58,65]

Although influenza B viruses are not categorized into subtypes based on HA and NA, they are divided into two distinct genetic lineages (Yamagata and Victoria) which have co-circulated since 1985 and comprise approximately 25% of positive influenza specimens in the U.S. Prior to the availability of quadrivalent influenza vaccines, which contain two B virus antigens derived from each of the two lineages, trivalent vaccines contained only one B virus antigen representing one lineage. During the ten seasons from 2001-2002 through 2010-2011, public health agencies were only able to correctly predict the predominant B lineage in five seasons, resulting in a mismatch between the vaccine and circulating strains for half of the 10-year period. The CDC estimated that in seasons where there is a B strain mismatch, the availability of a quadrivalent vaccine could result in an annual reduction of 2,200-970,000 influenza cases, 14-8,200 hospitalizations, and 1-485 deaths. In recent years, rates of hospitalization and mortality attributed to influenza B virus have been recognized as being lower than A/H3N2 but higher than A/H1N1, and, overall, similar to rates associated with seasonal influenza A viruses. The CDC estimates that 80%-90% of seasonal influenza-related deaths and 50%-70% of hospitalizations occur in adults ≥65 years. Thus, the disease burden of influenza B infections in the elderly is substantial. Vaccine coverage of both B strains is also desirable in young children who experience the highest mortality due to B strains. Although influenza B causes ~25% of all clinical disease, 34% of the 309 pediatric deaths reported to the CDC during 2004-2008 and 38% of 115 pediatric deaths reported during the 2010-2011 season were due to influenza B. One case series of autopsies on patients with fatal influenza B infections (including 32 mostly healthy children <18 years) demonstrated that the influenza B infections were severe and rapidly progressive, and that 69% of 29 cases with available cardiac tissue were associated with myocardial injury. The authors also observed an age-related difference in complications of influenza B disease. While 82% of deaths in adults ≥18 years were associated with bacterial superinfection, most (90%) of the influenza B deaths in children <18 years were associated with myocardial injury. In 2013, the World Health Organization (WHO) and the VRBPAC recommended the inclusion of a second influenza B vaccine virus antigen in quadrivalent influenza vaccines to provide coverage of both B lineages. Since the NH

2013-2014 influenza season, seven quadrivalent influenza vaccines have been licensed for use in the U.S. It is expected that, over time, quadrivalent formulations will become the standard of care for influenza vaccines. [6,16,18,48,65,68]

Since 1977, influenza A subtypes H1N1 and H3N2 and influenza B have co-circulated globally. Seasonal epidemics generally occur during the winter months and are caused by antigenic drift, new antigenic variants or viral strains that result from point mutations in the viral genome that occur during replication. Constant antigenic changes in the viral genome necessitate annual strain changes in the formulation of influenza vaccines for optimal protection. Neutralizing antibody against HA is the primary immune defense against infection with influenza. Although there is no established absolute immune correlate of protection, studies have suggested that HI titers of 1:32 to 1:40 correlate with protection against illness. This strain-specific immune response appears to predict a clinical endpoint of efficacy with reasonable certainty. Previous experience with inactivated influenza vaccines supports use of HI titers as a surrogate endpoint. [12,13,32,36,39,40,44]

The primary mode of controlling influenza disease is immunoprophylaxis. Because of the potential for serious and life-threatening influenza-related disease, the CDC's Advisory Committee on Immunization Practices (ACIP) has, over the last decade, broadened its recommendations for immunoprophylaxis of influenza and now recommends influenza vaccination for all persons 6 months of age and older without known contraindications. [12,16,19]

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

Five licensed antiviral agents are available in the U.S. for the prevention or treatment of influenza in persons with confirmed or suspected severe, complicated, or progressive influenza, or in those at higher risk for complications. Treatment of persons without known risk factors may also be considered if treatment can be initiated within 48 hours of onset or if infection with a novel influenza virus is suspected. Two older adamantane agents, amantadine and rimantidine, are active only against influenza A and are no longer recommended because of widespread resistance since 2005. One of three neuraminidase (NA) inhibitors, oseltamivir is an oral antiviral indicated for the treatment of influenza A and B in persons ≥ 14 days of age and for chemoprophylaxis in persons ≥1 year of age. Frequent gastrointestinal side effects may limit its usefulness. Emergence of resistance during treatment with oseltamivir was a problem for seasonal H1N1 viruses prior to their replacement by the 2009 pandemic H1N1-like strains which are now in circulation and only rarely resistant. Currently, seasonal H3N2 and B strains are also rarely resistant to oseltamivir. Zanamivir, another NA inhibitor, is indicated for treatment of influenza in persons ≥ 7 years of age and for chemoprophylaxis in persons ≥ 5 years of age. It is administered as an orally inhaled powder and is associated with bronchospasm especially in persons with underlying asthma or chronic obstructive pulmonary disease. It is rarely associated with resistance. The third NA inhibitor, peramivir, is a single dose intravenous antiviral indicated only for the treatment of acute uncomplicated influenza A and B viral infection in persons 2 years of age and older. Adverse effects include diarrhea. Postmarketing reports for NAs have also described serious cutaneous reactions and sporadic transient neuropsychiatric events. Due to concerns for potential emergence of resistance and adverse events, NA inhibitors are considered important adjuncts but not substitutes for vaccination. [15,17,19,28,36]

2.3 Safety and Efficacy of Pharmacologically Related Products

Licensed influenza vaccines available in the United States include: trivalent and quadrivalent inactivated influenza vaccines (IIV3 and IIV4), a trivalent and quadrivalent recombinant influenza vaccine (RIV3 and RIV4), a trivalent and quadrivalent live-attenuated influenza vaccine (LAIV3 and LAIV4), one high dose, and one adjuvanted trivalent inactivated vaccine. These vaccines are grown either in egg or cell culture. Not all licensed products are manufactured and distributed in any given influenza season, and, as quadrivalent influenza vaccines become the standard of care, some manufacturers no longer produce the trivalent formulations. Seven IIV3 [Afluria (5 years and older), Agriflu (18 years and older), Fluarix (3 years and older), FluLaval (6 months and older), Fluviron (4 years and older), Fluzone (6 months and older), and Flucelvax (4 years and older)] and five IIV4 [Afluria Quadrivalent (5 years and older), Fluarix Quadrivalent (6 months and older), FluLaval Quadrivalent (6 months and older), Fluzone Quadrivalent (6 months and older), and Flucelvax Quadrivalent (4 years and older)] standard dose (15 mcg HA per antigen) vaccines are approved for use in pediatric and adult populations. LAIV3 and LAIV4 (FluMist and FluMist Quadrivalent) are approved for use only in healthy non-pregnant persons 2 to 49 years of age. Intradermal IIV3 and IIV4 (Fluzone Intradermal and Fluzone Intradermal Quadrivalent) are limited to use in adults 18-64 years of age. RIV3 and RIV4 (Flublok and Flublok Quadrivalent) are approved for use in adults 18 years and older.

When vaccine and circulating viruses are antigenically well-matched, vaccination with IIV3 has been estimated as high as 70-90% effective in preventing influenza illness among young healthy adults < 65 years of age. More recent studies, including those that use polymerase chain reaction (PCR) methodology to confirm cases of influenza, estimate vaccine efficacy (VE) as being closer to 60%-70% and sometimes lower. Data in children are more limited than in younger adults but indicate similar rates of VE. One RCT to support approval in children was conducted for FluLaval Quadrivalent. In this trial, VE against all rt-PCR confirmed influenza illness in children 3-8 years was 55.4% (95% CI: 39.1%, 67.3%). Another RCT conducted to support approval of Fluarix Quadrivalent in children 6-35 months demonstrated a VE of 49.8% (95% CI: 41.8%, 56.8%) against all rt-PCR confirmed influenza illness, and a VE of 60.1% (95% CI: 49.1%, 69.0%) against antigenically-matched confirmed influenza. Estimates of VE and effectiveness are limited by a relative lack of randomized placebo-controlled trials, limitations associated with test negative case control observational designs, and dependence on multiple variables that change from one season to the next. Effectiveness is lower among persons with underlying illnesses, those ≥ 65 years of age, against the A/H3N2 subtype as compared to A/H1N1 and B strains, and when there is a poor antigenic match between vaccine and circulating influenza virus strains. Because of lower immune responses observed in the elderly, two other trivalent inactivated influenza vaccines with improved immunogenicity over standard IIVs were developed and licensed for use in adults ≥65 years of age: Fluzone High Dose (45 mcg HA per antigen) and Fluad [the first U.S.-licensed IIV3 (Agriflu) formulated with an adjuvant (MF59)]. [12,17,18,19,23,26,30,31,33,36,37,38,39,42,43,45,46,51,52,53,55,57,58,60,61,62,64,66,67,69,72,73,77,78]

Seasonal inactivated influenza vaccines (IIV) licensed for use in the U.S. have a long history of safety. The most common adverse events (AEs) associated with IIVs are local injection site reactions, e.g., pain, erythema, and induration. These reactions generally occur in >10% of patients, are usually mild to moderate in intensity, and are relatively short in duration (24-48 hours). Systemic symptoms following vaccination, e.g., fever,

arthralgia, myalgia, headache, are less common and, in RCTs, often occur at rates similar to those observed in placebo recipients making causality uncertain. [18,36,41,70,76]

Uncommon or rare AEs associated with influenza vaccines include neurologic events such as encephalitis, myelitis, and Guillain-Barre syndrome, and allergic or immediate hypersensitivity reactions, e.g., urticaria or angioedema. The incidence of anaphylaxis following IIV3 has been estimated as 1.35 cases per million doses (95% CI: 0.65, 2.47). [18,36,41,49,50,70,76]

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

Afluria QIV was initially approved for use in the U.S. in adults ≥18 years on August 26, 2016. Licensure was supported by a clinical trial (CSLCT-QIV-13-01) demonstrating non-inferior immunogenicity and safety as compared to Afluria TIV. Please see the clinical review of STN 125254/565 for additional information. Limited previous human experience with Afluria QIV in the pediatric population is derived from CSLCT-QIV-13-02, a clinical trial that supported US licensure in children 5 through 17 on August 31, 2017. Please see the clinical review of STN 125254/642 for additional information. At the time this efficacy supplement was submitted, the postmarketing experience for Afluria QIV was limited to adults ≥18 years in the U.S. and in Australia where the product was approved in adults ≥18 years on July 15, 2016 and was first made available during the Southern Hemisphere (SH) 2017 season. However, Seqirus TIV has been marketed in Australia and New Zealand since 1968 and globally since 1985 (by CSL Biotherapies, Inc and BioCSL Pty, Ltd, now known as Seqirus Pty, Ltd). Because they are manufactured by the same process, experience with the trivalent formulation informs and supports development of Afluria QIV. Please refer to Section 2.5 of this review, the Afluria Package Insert (PI) and the clinical reviews of STN 125254 Amendments 0, 132, and 259 for information regarding previous experience with Seqirus TIV in subjects 6 months and older.

Section 2.5 summarizes the regulatory history of Afluria TIV related to increased postmarketing reports of febrile seizures and other febrile events associated with the Southern Hemisphere (SH) 2010 formulation of Seqirus TIV. The background rate of febrile seizures is 2%-5% of children between 6 to 60 months, with a 3-fold higher risk in children 6-16 months. [1] The febrile seizure rate associated with the SH 2010 formulation of Seqirus TIV was up to 9 per 1,000 doses administered, ~9 times the expected rate. In response, on December 1, 2011, FDA restricted the indication for Afluria TIV to children ≥5 years while the Applicant pursued a scientific investigation to determine the root cause of the increased febrile adverse events. Previous clinical trial data regarding the rates of fever in children following vaccination with Seqirus TIV are relevant to the assessment of safety in the current pediatric efficacy supplement for Afluria QIV. Although there are limitations to comparisons across trials, to assist in placing the current data in context, Table 2 summarizes historical rates of fever from prior studies of Afluria TIV in pediatric age groups 6 through 59 months. Data from CSLCT-QIV-15-03, the study under current review, are included for ease of comparison.

Table 2: Historical and Current Rates of Fever following Afluria TIV, Afluria QIV, or Comparators in Children 6 through 35 months and 36 through 59 months*

Age Group Study (Year) Treatment	N	Dose 1 Any Fever ≥100.4°F (oral) ≥99.5°F (axillary) % (95% CI)	Dose 1 Fever ≥102.2°F (oral) ≥101.3°F (axillary) % (95%CI)	Dose 2 Any Fever ≥100.4°F (oral) ≥99.5°F (axillary) % (95% CI)	Dose 2 Fever ≥102.2°F (oral) ≥101.3°F (axillary) % (95%CI)	Strains (b) (4)
6-35 months CSLCT-FLU-04-05[1] (SH 2005) Afluria TIV	Dose 1 n=151 Dose 2 n=151	22.52 (16.13, 30.02)	2.65 (0.73, 6.64)	22.52 (16.13, 30.02)	7.8 (3.69, 12.66)	None
6-35 months CSLCT-USF-06-29 (SH 2009) Afluria TIV	Dose 1 n=703 Dose 2 n=615	28.59 (25.28), 32.09)	11.10 (8.87, 13.65)	17.89 (14.94, 21.15)	4.72 (3.18, 6.70)	None
6-35 months CSLCT-USF-07-36 (NH 2009-2010) Afluria TIV	Dose 1 n=229 Dose 2 n=96	37.12 (30.85, 43.73)	16.16 (11.64, 21.58)	14.58 (8.21, 23.26)	3.13 (0.65, 8.86)	None
6-35 months Pooled[2] Afluria TIV	Dose 1 n=1,083 Dose 2 n=862	29.55 (26.84, 32.36)	10.99 (9.19, 13.00)	18.33 (15.80, 21.08)	4.99 (3.63, 6.66)	None
6-35 months CSLCT-USF-07-36 Fluzone TIV	Dose 1 n=228 Dose 2 n=110	13.60 (9.43, 18.74)	3.51 (1.53, 6.80)	13.64 (7.84, 21.49)	3.64 (1.00, 9.05)	n/a[3]
6-35 months CSLCT-QIV-15-03 (NH 2016-2017) Afluria QIV	Dose 1 n=663 Dose 2 n=350	5.13 (3.58, 7.09)	1.66 (0.83, 2.95)	4.57 (2.64, 7.32)	1.71 (0.63, 3.69)	A/H1N1 A/H3N2 B/Yamagata B/Victoria
6-35 months CSLCT-QIV-15-03 Fluzone QIV	Dose 1 n=227 Dose 2 n=119	7.93 (4.77, 12.24)	1.32 (0.27, 3.81)	9.24 (4.71, 15.94)	3.36 (0.92, 8.38)	n/a[3]
36-59 months CSLCT-FLU-04-05[1] Afluria TIV	Dose 1 n=65 Dose 2 n=63	23.08 (13.53, 35.19)	6.15 (1.70, 15.01)	17.46 (9.05, 29.10)	0.00 (-, 5.69)	None
36-59 months CSLCT-USF-06-29 Afluria TIV	Dose 1 n=362 Dose 2 n=286	27.90 (23.34, 32.83)	9.39 (6.59, 12.88)	13.29 (9.58, 17.78)	4.55 (2.44, 7.65)	None
36-59 months CSLCT-USF-07-36 Afluria TIV	Dose 1 n=91 Dose 2 n=29	31.87 (22.49, 42.47)	15.38 (8.67, 24.46)	13.79 (3.89, 31.66)	3.45 (0.09, 17.76)	None
36-59 months Pooled[2] Afluria TIV	Dose 1 n=518 Dose 2 n=378	27.99 (24.16, 32.07)	10.04 (7.59, 12.96)	14.02 (10.68, 17.94)	3.70 (2.04, 6.14)	None
36-59 months CSLST-USF-07-36 Fluzone TIV	Dose 1 n=89 Dose 2 n=25	11.24 (5.52, 19.69)	1.12 (0.03, 6.10)	16.00 (4.54, 36.08)	0.00 (-, 13.72)	n/a[3]
36-59 months CSLCT-QIV-15-03 Afluria QIV	Dose 1 n=946 Dose 2 n=201	4.23 (3.04, 5.71)	1.16 (0.58, 2.07)	3.48 (1.41, 7.04)	0.50 (0.01, 2.74)	A/H1N1 A/H3N2 B/Yamagata B/Victoria
36-59 months CSLCT-QIV-15-03 Fluzone QIV	Dose 1 n=317 Dose 2 n=66	5.68 (3.40, 8.83)	0.95 (0.20, 2.74)	3.03 (0.37, 10.52)	0.00 (-, 5.44)	n/a[3]

Source: STN 125254/692.1, Module 1.11.3, Table 3, and 16 January 2018 telecon with Seqirus available in the Electronic Document Room.

Abbreviations: (b) (4) ; TIV=trivalent inactivated influenza vaccine; QIV=quadrivalent inactivated influenza vaccine; SH=Southern Hemisphere; NH=Northern Hemisphere.

Method of temperature measurements for Afluria TIV/QIV recipients: CSLCT-FLU-04-05: 6-35 months axillary 100%; 36-59 months axillary 94.9%, oral 5.1%. CSLCT-USF-06-29: 6-35 months axillary 98.5%,

oral 1.4%; 36-59 months axillary 95.8%, 4.2% oral. CSLCT-USF-07-36: 6-35 months axillary 89.2%, oral 10.8%; 36-59 months axillary 67.2%, oral 32.8%. CSLCT-QIV-15-03: 6-59 months axillary 100%. Method of temperature measurement for Comparator recipients: CSLCT-USF-07-36: 6-35 months axillary 89.8%, oral 9.9%; 36-59 months axillary 62.2%, oral 37.8%. CSLCT-QIV-15-03: 6-59 months axillary 100%.
*Analyses of children 36 through 59 months in studies CSLCT-FLU-04-05, CSLCT-USF-06-29, and CSLCT-USF-07-36 represent post-hoc subanalyses.
[1]Study CSLCT-FLU-04-05 has also been identified as CSLCT-NHF-04-05.
[2]Pooled Afluria TIV studies: CSLCT-FLU-04-05, CSLCT-USF-06-29, and CSLCT-USF-07-36 for 6-35 month and 36-59 month age groups.
[3]Comparator vaccine virus strains are (b) (4) .

Reviewer comment: Clinical trial data from earlier studies of Seqirus TIV [CSLCT-FLU-04-05 (SH 2005), CSLCT-USF-06-29 (SH 2009), and CSLCT-USF-07-36 (NH 2009-2010)] suggest that Seqirus TIV was more pyrogenic than other TIVs in children 6 through 59 months, even prior to the SH 2010 increased postmarketing reports of febrile seizures and febrile events. Rates of fever following the first vaccination with Afluria TIV or Fluzone TIV in children 6-35 months in CSLCT-USF-07-36 were 37.1% and 13.6%, respectively, and, for fever ≥102.2°F, 16.2% and 3.5%, respectively. Rates were lower in Afluria TIV recipients and similar in Fluzone TIV recipients following the second vaccination (14.6% and 13.6%, respectively). Rates of fever following the first vaccination with Afluria TIV or Fluzone TIV in children 36-59 months in CSLCT-USF-07-36 were 31.9% and 11.2%, respectively, and, for fever ≥102.2°F, 15.4% and 1.1%, respectively. Rates were lower in Afluria TIV recipients but higher in Fluzone TIV recipients following the second vaccination in the older age cohort (13.8% and 16.0%, respectively).

As a result of their febrile seizure investigation, the Applicant found that Seqirus TIV contained more residual viral lipids and RNA fragments than other TIVs. They demonstrated that viral lipids not only facilitated but were required for delivery of RNA fragments into host cells in vitro, which, in turn, stimulated the release of proinflammatory cytokines capable of mediating a pyrogenic response. The in vitro investigation also showed that (b) (4) and release of proinflammatory cytokines. The Applicant hypothesized that (b) (4) would reduce cytokine-mediated pyrogenicity in humans. To test this hypothesis in children, Seqirus conducted a Phase 4, randomized, observer-blind, comparator-controlled, multicenter safety study, CSLCT-USF-10-69, in 402 healthy children 5 through 8 years randomized 3:1 to receive Afluria TIV [NH 2014-2015 formulation manufactured using (b) (4) the A/H3N2 and B/Yamagata virus strains] or Fluzone QIV. The frequency and intensity of fever over the seven days following each vaccination was the primary endpoint. Results showed that overall rates of fever were similar between treatment groups, and revealed a trend towards more moderate and severe fever in the Fluzone QIV group. The rates of any fever (≥100.4°F) and severe fever (defined as ≥102.2°F) following the first dose of Afluria TIV were 8.2% and 2.1%, respectively. No subjects reported fever following a second dose of Afluria TIV. The rates of any fever and severe fever following the first dose of Fluzone QIV were 8.2% and 3.1%, respectively, and, following a second dose, 5.1% (all cases were severe). Data from CSLCT-USF-10-69 demonstrated lower rates of fever and severe fever compared to historical rates observed in previous Afluria TIV pediatric studies (see the clinical review of STN 125254.642 for historical rates of fever in children 5-8 years), and suggested that the lower rates might be related to (b) (4) of the vaccine virus strains (A/H3N2 and B/Yamagata) with (b) (4) .

CSLCT-USF-10-69 supported the Applicant's decision to move forward with study CSLCT-QIV-13-02, a study of Afluria QIV, all four strains (b) (4) , as compared to a U.S.-licensed IIV4 (Fluarix Quadrivalent) in children 5 through 17 years. Among children 5 through 8 years in CSLCT-QIV-13-02 who received Afluria QIV, rates of fever in the seven days following the first and second vaccinations were 4.0% and 2.2%, respectively, as compared to 3.0% and 3.2%, respectively, for recipients of Fluarix QIV. No febrile seizures were reported, and rates of other solicited systemic symptoms were similar between treatment groups. Afluria QIV recipients 5 through 8 years had slightly higher rates of local reactogenicity as compared to Fluarix QIV, but overall rates were low. One 8-year-old recipient of Afluria QIV had a cellulitis-like reaction (concurrent Grade 3/severe injection site pain, swelling and redness), but recovered without sequelae. No vaccine-related SAEs or discontinuations due to AEs occurred following Afluria QIV in study CSLCT-QIV-13-02. The data supported approval of Afluria QIV in children and adolescents 5 through 17 years on August 31, 2016. Please see the clinical review of STN 125254/642 for additional information.

Reviewer comment: Data from CSLCT-QIV-13-02 demonstrated much lower rates of fever, similar to the U.S.-licensed comparator, relative to historical rates reported prior to (b) (4) ***all virus strains with*** (b) (4) ***. Nevertheless, the Applicant designed CSLCT-QIV-15-03 with stringent halting rules and downward phased enrollment with close Data Safety Monitoring Board review of safety.***

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

The original sponsor of CSLCT-QIV-15-03 was bioCSL Pty, Ltd. On November 9, 2015, bioCSL began operating under the name Seqirus Pty, Ltd following a merger between Novartis' influenza vaccine business and bioCSL. Seqirus is the current Applicant.

- September 28, 2007 – STN 125254/0. Accelerated approval was granted to Afluria (trivalent formulation) for use in adults 18 years and older.
- November 10, 2009 – STN 125254/132. Accelerated approval was extended to children 6 months through 17 years during the 2009 H1N1 influenza pandemic so that a second pandemic vaccine would be available for children 6 months through 2 years.
- July 2010 – The Afluria PI was modified with a warning regarding use in children <5 years due to increased postmarketing reports of fever and febrile seizures associated with the SH 2010 formulation of Afluria (Fluvax) predominantly in children <5 years. Please see the clinical review of STN 125254/181.1 for details. Since the 2010 febrile seizures and events in children, the use of Seqirus TIV, including Afluria, has been restricted globally to children ≥5 years.
- July 2010 Postmarketing Requirement (PMR) – CBER requested that Seqirus design a postmarketing study to assess fever and febrile events in children 5 to < 9 years because of the new safety signal.
- February 2011 – CBER released CSL from the July 2010 PMR, invoking the "good cause" argument from Title IX of FDAAA 2007 [(505(o)(3)(E)(ii)], after determining that conduct of the study was not feasible until a scientific investigation into the root cause of the SH 2010 febrile events was completed.
- July 15, 2011 – The Indications and Usage of the Afluria PI was changed to persons 5 years and older due to the increased postmarketing reports of fever and febrile seizures associated with the SH 2010 formulation.

- December 2, 2011 – Traditional approval of Afluria was granted in adults ≥18 years [based on fulfillment of postmarketing commitments (PMCs) to conduct a clinical endpoint study in adults 18 through 64 years and studies of safety and non-inferior immunogenicity in adults ≥65 years] and in children and adolescents 5 through 17 years (based on fulfillment of PMCs to conduct studies of safety and non-inferior immunogenicity). Please see the clinical review of efficacy supplement STN 125254/259 for details.
- March 12, 2013 – Pre-IND meeting with Seqirus to discuss the Afluria QIV clinical development plan (CRMTS#8832; PTS#1965, IND 15974). Please see the meeting summary for details.
- April 4, 2013 – Labeling supplement (STN 125254/440). Section 6.2 (Postmarketing Experience) of the Afluria PI was revised to include "cellulitis and large injection site swelling".
- December 2013 – IND 12297/130. Final summary of Seqirus' scientific investigation into the root cause of the SH 2010 febrile seizures. Please see Section 2.4.
- March 28, 2014 – An adult QIV protocol CSLCT-QIV-13-01 and an initial Pediatric Study Plan (iPSP) were submitted to IND 15974/0. The general investigative plan included a proposal to conduct a small safety study (CSLCT-USF-10-69) of Afluria TIV in children 5 through 8 years concurrent with CSLCT-QIV-13-01, using (b) (4) than previously (b) (4) the A/H3N2 and B strains, prior to conducting a larger study of Afluria QIV in children 5 through 17 years of age (CSLCT-QIV-13-02). Please see Section 2.4.
- August 8, 2014 – The Applicant submitted an agreed iPSP incorporating CBER's recommendations to IND 15974/4. Please see Section 9.1.3 for details.
- April 21, 2015 – A pre-sBLA meeting was held to discuss the submission of STN 125254/565, efficacy supplement for Afluria QIV in adults ≥18 years and the study design for CSLCT-QIV-13-02 (pediatric subjects 5-17 years).
- February 10, 2016 – The PeRC concurred with the final PSP submitted to STN 125254/565. Please see Section 9.1.3 for details.
- May 11, 2016 – A Type B meeting was held to discuss completed (CSLCT-QIV-13-02) and planned (CSLCT-QIV-15-03) Afluria QIV pediatric studies. Please see meeting summary for details (CRMTS #10232, IND 15974/32). Protocol CSLCT-QIV-15-03 was subsequently submitted to IND 15974/34.
- August 26, 2016 – Afluria QIV was approved in adults ≥18 years (STN 125254/565).
- August 31, 2017 – Afluria QIV was approved in children and adolescents 5 through 17 years (STN 125254/642).
- August 7, 2018 – The review team determined that Seqirus' response to an Information Request regarding the BIMO inspection of CSLCT-QIV-15-03 clinical study site #8400445 (STN 125254/692.14) constituted a major amendment, and the Action Due Date for the supplement was extended to December 1, 2018. Please see Section 3.2 for details.

2.6 Other Relevant Background Information

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate conduct of a complete clinical review.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The Applicant stated that the protocol was written and conducted in compliance with the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, U.S. federal regulations, and local ethical and regulatory requirements. These requirements included IRB approval of the protocol and the informed consent of parents and guardians.

Bioresearch Monitoring (BIMO), Division of Inspections and Surveillance, Office of Compliance and Biologics Quality, conducted an inspection of three clinical study sites representing 10.7% of the FAS (sites #8400427, #8400428, and #8400445). Inspections at sites #8400427 and #8400428 found no deficiencies that would preclude approval.

The BIMO Establishment Inspection Report (EIR) for study site #8400445 was made available to the review team on July 16, 2018. Site #8400445 included 69 vaccinated subjects (Afluria QIV n=54; Comparator QIV n=15). The EIR noted numerous protocol deviations (discovered by site monitors and reported to the sponsor), incomplete and/or inaccurate source documents, and lack of contemporaneousness in documentation, raising questions about the quality and integrity of the data. For example, 20 of 69 vaccinated subjects were enrolled despite having active infections in violation of protocol exclusion criterion #5 (n=19) or inclusion criterion #3 (n=1), constituting major protocol deviations. Three subjects were receiving oral corticosteroids, prohibited medications, at enrollment, another major deviation. Of twenty-four records evaluated: eight subjects had improper documentation of informed consent; nine subjects had an unnecessary blood draw; five subjects were randomized to an improper dose regimen (one versus two); and eight subjects did not have or had an out-of-window Day 3 phone contact. Please see the BIMO review for details. Regarding reports to the sponsor, the inspector noted that all reports and data submitted to the Contract Research Organization (CRO) and the sponsor via the eCRF, electronic data capture (EDC) system, and site monitor visits, appeared on time and complete. The EIR was reviewed in detail as were the data for subjects at this site. All protocol deviations noted in the EIR were reported in the Complete Study Report (CSR) tables and listings, Statistical Analysis Plan (SAP) listings, and electronic datasets.

To address concerns regarding the quality and integrity of the data, the clinical review team requested information from the sponsor, including a rationale for not excluding the site from the final study analyses and not highlighting problems noted at the site in the body of the CSR. The sponsor was also asked to provide repeat demographic, immunogenicity and safety analyses excluding site #8400445. The sponsor's response to our information request (please see STN 125254/692 Amendments 13 and 14), 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. Subjects appeared to have been appropriately excluded from the immunogenicity populations according to the protocol and Statistical Analysis Plan (SAP). Of 69 vaccinated subjects, 41 (59.4%)

were included in the Per Protocol Population (PPP) as compared to 86.3% of subjects included the PPP for the entire study. The sponsor also noted that solicited and unsolicited adverse events were entered into electronic diaries by parents and/or guardians in real time, independent of the site investigators, and that the sponsor monitored electronic diary completion rates on a weekly basis. The electronic diary completion rate for the site was 80% deemed high and comparable to 87% for the entire study population. Overall, 62 of 69 vaccinated subjects (89.9%) provided safety information and were included in the Safety Population (SP).

The sponsor's repeat analyses excluding site #8400445 were reviewed in detail. The FDA statistical reviewer also provided repeat primary immunogenicity analyses and summary safety analyses excluding the site. Site #8400445 represented a small proportion of the total study data [3.1% (69 of 2232) of the SP and 2.1% (41 of 1940) of the PPP]. For the primary immunogenicity analysis, differences between results reported in the CSR (all study sites) and repeat analyses excluding site #8400445 were no more than 0.02 for upper bounds (UB) on the 95% confidence intervals (CI) for geometric mean titer (GMT) ratios, and no more than 0.9% for UBs on the 95% CIs for seroconversion rate (SCR) differences. The primary endpoint would have been met had site #8400445 been excluded. Regarding safety data, repeat analyses performed both by the sponsor and the statistical reviewer demonstrated that exclusion of site #8400445 yielded minimal differences in the rates of any solicited or unsolicited AE overall, specific event rates, and rates according to severity grade or relatedness. For the vast majority of events, including solicited local and systemic AEs and fever, rates of specific events in the repeat analyses excluding site #8400445 were identical or differed only by 0.1%-0.2% as compared to the rates for the entire study population reported in the CSR. Only one AE event parameter differed by as much as 0.7% (All Afluria QIV recipients 6-35 months who reported any AE in the system organ class of Infections and Infestations, 18.0% for the entire study, 17.3% excluding site #8400445). The clinical reviewer also reviewed safety data for site #8400445 by evaluating the electronic datasets and confirmed that rates and severity of solicited and unsolicited AEs were generally comparable to the entire study population. No serious adverse events (SAEs) or discontinuations due to AEs were reported. Only one subject (35-59 months) from site #8400445 reported a severe but non-serious AE, solicited nausea and vomiting, beginning two days post-vaccination and ending on the same day.

The clinical reviewers acknowledged BIMO's decision to recommend exclusion of site #8400445. However, considering the sponsor's enhanced site monitoring ensuring that data were entered into the clinical database, appropriate exclusion of major protocol deviations, and minimal differences between final analyses reported in the CSR and repeat analyses excluding site #8400445, the clinical review team agreed with the sponsor's decision to allow site #8400445 to continue in the study and to include the study in the final analyses. Analyses excluding site #8400445 had no clinically significant impact on the overall interpretation of the study data, and the clinical review team elected to present safety data from the entire Safety Population in the clinical review and Package Insert. The statistical reviewer agreed with this approach. Please see the BIMO and statistical reviews for additional information.

3.3 Financial Disclosures

The Applicant provided a signed Form FDA 3454 and a list of investigators for the clinical study submitted to the sBLA, and certified that they had not entered into any

financial agreements with the investigators that could potentially influence the outcome of the study. The Applicant certified further that each listed investigator was required to disclose their financial interests and that no disclosable financial interests or arrangements as defined by 21 CFR 54.2 were reported.

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

4.1 Chemistry, Manufacturing, and Controls

The Chemistry, Manufacturing, and Controls (CMC) review team identified no issues that would preclude licensure. Regarding the Applicant's scientific investigation into the root cause of the SH 2010 febrile adverse events (see Section 2.4), CMC noted that the Applicant identified a plausible molecular mechanism responsible for the induction of fever and then developed novel assays to characterize and reduce the reactogenic potential of the monovalent (b) (4) harvest ((b) (4) or drug substance). Steps taken to address issues identified in the Applicant's scientific investigation included: 1) (b) (4) which plays a key role in cytokine induction; 2) development of a novel assay to measure residual lipid content during manufacture of the drug substance; and 3) development of a novel assay to measure the percentage of (b) (4) virus in the (b) (4). During labeling discussions, DVP indicated that, in their view, the improved control and testing of the manufacturing process and the clinical studies demonstrating lower rates of fever using the modified process supported removal of the description of the SH 2010 febrile events from the PI. Please see the CMC review and Section 11.5 (Labeling Review and Recommendations) for additional discussion.

4.2 Assay Validation

The hemagglutination inhibition (HI) assays and reverse transcriptase polymerase chain reaction (rtPCR) tests were performed by (b) (4) . The statistical assay reviewer identified no significant deficiencies in regard to the HI assay validation data submitted to the sBLA. Please see the statistical and DVP reviews for details.

4.3 Nonclinical Pharmacology/Toxicology

Because Afluria QIV is manufactured by the same process as the trivalent formulation and differs only in an additional B strain, CBER informed the Applicant that no additional non-clinical or toxicology data were required to support the clinical development of Afluria QIV. Please see the March 12, 2013 pre-IND meeting summary for details.

4.4 Clinical Pharmacology

Not applicable.

4.4.1 Mechanism of Action

Vaccination with inactivated influenza vaccines induces antibody responses primarily against HA and NA. Strain-specific neutralizing antibodies against HA provide the main protection against infection and clinical disease. The anti-HA antibody response, measured by the hemagglutination inhibition (HI) assay, is currently the best available surrogate marker of activity that is reasonably likely to predict clinical benefit. To date, prospective studies have not identified a specific HI titer associated with protection against culture confirmed influenza illness. Some studies have shown that HI titers

ranging from 1:32 to 1:40 are associated with protection from illness in approximately 50% of subjects, and that protection from illness generally correlates with higher titers. However, no single HI titer has been identified that predicts protection. [12,13,32,36,39,40,44,67]

Reviewer comment: NA inhibits viral replication by preventing release of new virions from the infected cell surface. Anti-NA antibodies block this action and have been shown to independently correlate with protection and reduction in disease severity. However, the NA content of currently licensed influenza vaccines is not standardized. Other non-neutralizing antibodies, e.g., to the ectodomain of matrix protein (M2e), and/or cellular responses, e.g., to internal nuclear protein (NP) and matrix protein M1, to vaccination may also contribute to protection but are not measured or standardized in approved IIVs.[34,47,54,56]

4.4.2 Human Pharmacodynamics (PD)

Not applicable.

4.4.3 Human Pharmacokinetics (PK)

Not applicable.

4.5 Statistical

Please see the statistical review. The statistical reviewer identified no issues that would preclude approval of the supplement.

4.6 Pharmacovigilance

Please see the OBE/DE review of the Pharmacovigilance Plan (PVP). At the time the clinical review was completed, the OBE/DE reviewer had identified no safety concerns that would require a postmarketing study (PMR) designed specifically to evaluate a safety endpoint, and did not recommend a risk evaluation and mitigation strategy (REMS) as necessary for Afluria QIV. The Applicant 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. Please see the OBE/DE review for additional information.

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

5.1 Review Strategy

Seqirus conducted one pivotal study, CSLCT-QIV-15-03, to support licensure of Afluria QIV in children 6 through 59 months. The reviewer evaluated the study data for consistency with information included in the proposed PI. Study designs, endpoints, and statistical methods used in CSLCT-QIV-15-03 were similar to those which supported licensure of Afluria (TIV) and of Afluria QIV in adults ≥18 years and children and adolescents 5 through 17 years. Non-inferior immune responses elicited by Afluria QIV as compared to Comparator QIV were considered adequate to infer clinical benefit based on the clinical endpoint data that supported licensure of Afluria (TIV) in adults ≥18 years. Because the vaccines are manufactured by the same process and have overlapping compositions, the clinical efficacy data for Afluria (TIV) are relevant to Afluria QIV and were included in the proposed PI. Regarding safety, the occurrence of fever following Afluria QIV was of special interest and was compared not only to the

comparator control but to historical rates of fever collected in similarly designed studies conducted by the Applicant (Section 2.4).

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

- STN 125254/692.0 – Modules 1, 2, and 5, and associated datasets.
- STN 125254/692.1 – Response to 11/21/17 IR – Historical rates of fever following Afluria IIV; site enrollment.
- January 16, 2018 telecon (located in EDR) with Seqirus to clarify STN 125254/692.1, Module 1.11.3, Table 3 responses regarding historical rates of fever.
- STN 125254/692.2 – Response to 12/13/17 IR, items #1 (partial), 2, 3, and 4, to correct errors in immunogenicity and safety Tables 11.4-1 and 12.2.2-4 and package insert Table 10.
- STN 125254/692.3 – Response to 12/13/2017 IR, item #1, request for updated Package Insert (PI) for Afluria (trivalent formulation) and plans for licensure of Afluria in persons 6-59 months.
- STN 125254/692.4 – Response to 1/24/18 IR – ADAE dataset and fever CRFs.
- STN 125254/692.5 – Response to 2/8/18 IR – Antipyretic use analyses, postmarketing exposure, non-U.S. licensures, database lock, central laboratory.
- STN 125254/692.6 – Responses to 2/13/18 and 2/15/18 IRs – Requests for an annotated QIV PI and additional information on Subject #(b) (6) .
- STN 125254/692.8 – Response to 3/28/18 IR – Clarification of subjects excluded from unsolicited and solicited local AE analyses.
- STN 125254/692.9 – Response to 4/20/18 IR, revised QIV and TIV PIs.
- STN 125254/692.10 – Response to 5/30/18 IR, revised QIV and TIV PIs.
- STN 125254/692.11 – Response to 6/4/18 IR, updated Risk Management Plan.
- STN 125254/692.13 – Response to 7/23/18 IR, site #8400445, items 1-3.
- STN 125254/692/14 – Response to 7/23/18 IR, site #8400445, items 4-6.

5.3 Table of Studies/Clinical Trials

Table 3 presents the characteristics of the single clinical study submitted to support licensure of Afluria QIV in a pediatric population 6 through 59 months.

Table 3: Summary of Clinical Trials Submitted to STN 125254/692

Study ID NCT# Season Location	Design	Population Enrolled*	Objectives	Endpoints**	Analysis Populations
CSLCT-QIV-15-03 NCT 02914275 NH 2016-2017 USA and Canada	Phase 3, observer-blind, comparator-controlled, multicenter study, stratified by age (6-35 and 36-59 months), randomized 3:1 to receive one or two 0.25 mL or 0.5 mL doses (depending on age and vaccination history) of Afluria QIV or U.S.-licensed Comparator QIV, administered IM 28 days apart. 0.25 mL dose = 7.5 mcg HA per strain, in children 6-35 months. 0.5 mL dose = 15 mcg HA per strain, in children 36-59 months.	Healthy children 6-59 months 2247 Total 1684 Afluria QIV 563 Comparator QIV	Non-inferior immunogenicity Safety	Co-primary: GMT ratio and SCR difference for each strain. Secondary: Post-vaccination GMTs, % HI titer ≥1:40, SCRs ***Frequency and severity of solicited AEs (7 days), cellulitis-like injection site reactions (28 days), unsolicited AEs (28 days), and SAEs (180 days)	Safety: 2232 Total; 1673 Afluria QIV; 559 Comparator QIV Per Protocol 1940 Total; 1456 Afluria QIV; 484 Comparator QIV

Source: Adapted from STN 125254/692, Module 5, CSLCT-QIV-15-03 CSR text and Tables 5.2-1 and 14.1.1.1.
NCT=ClinicalTrials.gov identifier; NH=Northern Hemisphere; IM=intramuscular; QIV=quadrivalent influenza vaccine; Comparator QIV=Fluzone Quadrivalent; HA=hemagglutinin; GMT=geometric mean titers; SCR=seroconversion rate; HI=hemagglutination inhibition; AE=adverse event; SAE=serious adverse event.
*Full Analysis Set
**Immunogenicity assessed at 28 days after the final vaccination. The Per Protocol Population was used for the primary immunogenicity analysis.
***After each vaccination, if applicable

5.4 Consultations

Not applicable.

5.4.1 Advisory Committee Meeting

Not applicable.

5.4.2 External Consults/Collaborations

Not applicable.

5.5 Literature Reviewed

1American Academy of Pediatrics. Febrile Seizures: Clinical Practice Guideline for the Long-term Management of the Child with Simple Febrile Seizures. Pediatrics 2008;121:1281-1286.

2American College of Obstetricians and Gynecologists Frequently Asked Questions: Miscarriage and Molar Pregnancy; 2011.

3Atmar RL, et al. Influenza vaccination of patients receiving statins: Where do we go from here? J Infect Dis 2016;213:1211-1213.

4Avalos LA, et al. A systematic review to calculate background miscarriage rates using life table analysis. Birth Defects Research 2012;94:417-423.

5Belongia EA, et al. Waning vaccine protection against influenza A (H3N2) in children and older adults during a single season. Vaccine 2015;33:246-251.

6Belshe RB, et al. Efficacy of live attenuated influenza vaccine in children against influenza B viruses by lineage and antigenic similarity. Vaccine 2010;28:2149-56.

7Bhat N, et al. Influenza-associated deaths among children in the United States, 2003-2004. N Engl J Med 2005;353:2559-67.

8Black S, et al. Influence of Statins on Influenza Vaccine Response in Elderly Individuals. J Infect Dis 2016;213:1224-1228.

9Black S, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunization with pandemic H1N1 influenza vaccines. Lancet 2009;374:2115-22.

10Castilla J, et al. Decline in influenza vaccine effectiveness with time after vaccination, Navarre, Spain, season 2011/12. Euro Surveill. 2013;18(5):pii=20388. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20388

11Centers for Disease Control and Prevention. Estimates of Death Associated with Seasonal Influenza – United States, 1976-2007. MMWR 2010;59(33): 1057-1062.

12Centers for Disease Control and Prevention. Prevention and Control of Influenza. Recommendations of the Advisory Committee on Immunization Practices. MMWR 2008;57(RR-7): 1-60.

13Centers for Disease Control and Prevention. Prevention and Control of Influenza. Recommendations of the Advisory Committee on Immunization Practices. MMWR 2009;58(RR-8): 1-52.

14Centers for Disease Control and Prevention. Update: Recommendations of the Advisory Committee on Immunization Practices (ACIP) Regarding the Use of CSL Seasonal Influenza Vaccine (Afluria) in the United States During 2010-11. MMWR 2010;59:989-992.

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16Centers for Disease Control and Prevention. Prevention and Control of Seasonal Influenza with Vaccines. Recommendations of the Advisory Committee on Immunization Practices – United States, 2013-2014. MMWR 2013;62:(RR-7). September 30, 2013.

17Centers for Disease Control and Prevention. Interim adjusted estimates of seasonal influenza vaccine effectiveness – United States, February 2013. MMWR62:(7)119-123.

18Centers for Disease Control and Prevention MMWR Weekly: Influenza Activity – United States, 2012-2013 Season and Composition of the 2013-2014 Influenza Vaccine. MMWR 2013;62(23):473-479.

19Centers for Disease Control and Prevention. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the ACIP, United States, 2014-15 Influenza Season. MMWR 2014;63(RR-32).

20Centers for Disease Control and Prevention. Early Estimates of Seasonal Influenza Vaccine Effectiveness – United States, January 2015. MMWR 2015;64:10-15.

21Centers for Disease Control and Prevention. Influenza Activity – United States, 2014-15 Season and Composition of the 2015-16 Influenza Vaccine. MMWR 2015;64:583-590.

22Centers for Disease Control and Prevention. Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2015-16 Influenza Season. MMWR 2015;RR64:818-825.

23Centers for Disease Control and Prevention. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the ACIP, United States, 2016-17 Influenza Season. MMWR 2016;65(RR-05).

24Centers for Disease Control and Prevention. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP) – United States 2017-18. MMWR 2017;66:1-20 and Background Document 66:1-77.

25Centers for Disease Control and Prevention. Update Influenza Activity – United States, October 1, 2017 – February 3, 2018 and Interim Estimates of 2017-18 Seasonal Influenza Vaccine Effectiveness – United States, February 2018. MMWR 2018;67:169-185.

26Centers for Disease Control and Prevention. End of Season Influenza Vaccine Effectiveness Estimates for the 2014-15 Season: U.S. Influenza Vaccine Effectiveness (Flu VE) Network, presented by Brendan Flannery, Ph.D., to the Advisory Committee for Immunization Practices (ACIP) on June 24, 2015. Accessed on February 20, 2016 at: http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2015-06/flu-02-flannery.pdf

27Centers for Disease Control and Prevention. Disease Burden of Influenza. Accessed on April 20, 2017 at https://www.cdc.gov/flu/about/disease/burden.htm

28Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians, accessed on February 21, 2017 at http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm .

29Centers for Disease Control and Prevention. FluView. Influenza-Associated Pediatric Mortality. 2018. Accessed on 2/16/18 at https://www.cdc.gov/flu/weekly/pastreports.htm

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6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1

"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 U.S.-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 U.S.-licensed 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 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 U.S.-licensed comparator QIV in two age strata: 6 months through 35 months, and 36 months through 59 months, as well as overall.

Exploratory Objective

To assess the frequency of antipyretic use in the first 7 days post-vaccination in two age strata: 6 months through 35 months, and 36 months through 59 months, as well as overall according to treatment group.

6.1.2 Design Overview

CSLCT-QIV-15-03 was a Phase 3, randomized, observer-blinded, comparator-controlled, multicenter study of Seqirus QIV versus U.S.-licensed 2016-2017 comparator QIV containing the same influenza strains recommended by the VRBPAC for the NH 2016-2017 influenza season. The study was conducted in the NH 2016-2017 influenza season in generally healthy male and female subjects with medically stable common comorbid conditions (planned n=2222) 6 through 59 months, stratified into two age cohorts, 6 through 35 (Cohort A) and 36 through 59 (Cohort B) months, using a quota to ensure that no more than 60% of the total sample size was represented in either age stratum. Enrollment and randomization began with subjects in the 36 through 59 months age group. After a minimum of 300 subjects had received the first vaccination and provided at least 7 days of post-vaccination safety data, a Data Safety Monitoring Board (DSMB) reviewed the safety data to provide a recommendation on whether enrollment in the 6 through 35 months age group could begin. A second DSMB review was performed after a minimum of 300 subjects in the 6 through 35 months age group had received the first vaccination and provided at least 7 days of post-vaccination safety data.

Following parental or guardian informed consent, subjects were screened for eligibility within a maximum of 7 days prior to intramuscular (IM) administration of study vaccination on Day 1. Eligible subjects were enrolled and stratified as described, and randomized 3:1 to receive either Seqirus QIV or Comparator QIV in a regimen of one or two vaccinations 28 days apart. Dose and dosing regimen depended on age and prior vaccination history as recommended by the ACIP for the 2016-2017 influenza season. Children 6 through 35 months received a 0.25 mL dose while children 36 through 59 months received a full adult dose of 0.5 mL with each vaccination. For subjects who previously received two or more doses of a U.S.-licensed trivalent or quadrivalent influenza vaccine before July 1, 2016, only one dose of study vaccine was administered. Subjects who had not previously received at least two doses of TIV or QIV before July 1, 2016 were eligible to receive two doses 28 days apart.

Blood samples for HI antibody titers were collected prior to the first vaccination and 28 days (+4) after the last study vaccination. Parents or guardians recorded prespecified solicited local and systemic symptoms and temperature for 7 days (Day 1 through Day 7), and unsolicited AEs for at least 28 days, following each vaccination in electronic diaries. Cellulitis-like reactions, defined as concurrent Grade 3 injection site pain, erythema, and induration, were monitored for 28 days after each vaccination. Serious adverse events (SAEs) and adverse events of special interest (AESIs), defined as medically significant events associated with the pharmacologic class of influenza vaccines, were monitored for 180 days after the last vaccination.

Subjects returned to clinic 28 days after each vaccination to review solicited and unsolicited AEs and concomitant medications. SAEs were collected at clinic visits and via telephone contacts at least 90 and 180 days after the last vaccination. Parents and guardians were instructed to contact the study site immediately if the subject experienced a cellulitis-like reaction or influenza-like illness (ILI). Subjects were asked to attend an additional clinic visit within 24 or 72 hours of onset of a cellulitis-like reaction or ILI, respectively.

Reviewer comment: The study was similar in design to studies supporting licensure of other quadrivalent influenza vaccines, and was agreed upon in a pre-

sBLA meeting held with the Applicant on May 11, 2016 followed by submission of the study protocol (IND 15974/34). FDA required a U.S.-licensed comparator QIV which the Applicant selected based on availability. Eligible subjects were randomized by means of a computer-generated program to ensure balance between treatment groups, a 3:1 randomization, and stratification of no more than 60% of subjects in each age cohort. The randomization code was prepared by a company independent of the Applicant to ensure that the blind was maintained. The investigator, study site staff, all personnel performing assessments, parents, guardians, and subjects were blinded to treatment. The randomization code was unblinded and provided to the biostatisticians only after all subjects completed immunogenicity, solicited, and unsolicited AE assessments, after the database lock, and at the time of the first planned interim analysis. Subjects and study staff remained blinded through the long term SAE follow-up and final database lock and analyses. Please see Section 6.1.9, Statistical Considerations and Statistical Analysis Plan, for additional information. The randomization and blinding procedures were deemed adequate by both the clinical and statistical reviewers.

Reviewer comment: During the 2011 SH influenza season, the Applicant's routine safety surveillance system identified increased reports of large/extensive injection site swelling and cellulitis-like reactions associated with the use of Afluria TIV. These events ("cellulitis and large injection site swelling") were subsequently included in Section 6.2 (Postmarketing Experience) of the Afluria PI. During the March 12, 2013 pre-IND meeting for Afluria QIV, FDA requested monitoring of such events in the QIV development program. Thus, CSCT-QIV-15-03 included a pre-specified safety endpoint of the occurrence of cellulitis-like reactions in the 28 day period post-vaccination. The Applicant's routine postmarketing surveillance includes monitoring and reporting of "large/extensive injection site swelling" and "cellulitis-like reactions" to FDA in the annual Drug Safety Update Report (DSUR). Seqirus has also added these AEs as "important potential risks" to its PVP.

6.1.3 Population

Selected Inclusion Criteria

- Males or females 6 through 59 months, born between 36 and 42 weeks gestation, in general good health in the judgment of the investigator.
- Parents or legally acceptable representative able to provide informed consent and adhere to protocol requirements.

Selected Exclusion Criteria

- History of allergic reactions to egg proteins or any study vaccine components.
- History of serious adverse reactions to any influenza vaccines.
- History of Guillain Barre Syndrome (GBS) or other demyelinating diseases.
- History of licensed influenza vaccine in the last six months.
- Signs of active infection and/or axillary temperature ≥99.5°F (37.5°C) within 48 hours of vaccination. Study entry could be deferred for such individuals, at the discretion of the investigator.
- Current or recent acute or chronic medical conditions that in the opinion of the investigator are clinically significant and/or unstable within the preceding 30 days (e.g., required hospitalization; associated with significant organ deterioration; associated with major changes in treatment dosages; or required major new treatments).
- History of any seizure, with the exception of a single febrile seizure.

- History of Human Immunodeficiency Virus (HIV), hepatitis B, or hepatitis C.
- Immunosuppressive conditions or therapies in the three months prior to vaccination. Topical or inhaled corticosteroids prior to vaccination or throughout the study were acceptable.
- Administration of immunoglobulin or any blood products within 90 days prior to the first study vaccination or planned administration during the study.
- Receipt of or plans to receive a live or inactivated licensed vaccine 21 days prior to administration of study vaccine, or through the 28 days following the last study vaccine.
- Participation/planned participation in a clinical trial or use/planned use of an investigational product 28 days prior to through 28 days after the final study vaccination.
- Conditions or treatments associated with an increased risk of bleeding except for antiplatelet agents such as low-dose aspirin, ticlopidine and clopidogrel.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Both study vaccines were inactivated split virion quadrivalent influenza vaccines. A single 0.25 mL or 0.5 mL dose of each vaccine contained 7.5 mcg or 15 mcg of HA antigen, respectively, for each of the 4 strains recommended by FDA's VRBPAC for the NH 2016-2017 influenza season (total HA = 30 mcg or 60 mcg, respectively). Both vaccines were supplied as thimerosal-free suspensions in needleless pre-filled syringes, and were administered intramuscularly (IM) into the anterolateral aspect of the thigh (or the deltoid muscle of the arm if muscle mass was adequate) in children 12 through 35 months, or the deltoid region of the non-dominant arm in children 36 through 59 months. Vaccines were administered either as a single 0.25 mL (6 through 35 months) or 0.5 mL (36 through 59 months) dose, or as two doses 28 days apart depending on previous vaccination history.

The four influenza strains recommended by FDA's VRBPAC for the NH 2016-2017 season quadrivalent vaccines were:

- 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)
- B/Phuket/3073/2013-like virus (B/Yamagata lineage)

Afluria QIV
Lot Numbers: 090403501 (0.25 mL) and 090403502 (0.5 mL)

U.S.-Licensed Comparator QIV (Fluzone Quadrivalent, Sanofi Pasteur)
Lot Numbers: UT5583UA (0.25 mL) and UI683AA (0.5 mL)

6.1.5 Directions for Use

Not applicable.

6.1.6 Sites and Centers

CSLCT-QIV-15-03 was conducted at 39 centers across the U.S. Study sites and the principal investigator for each site are presented in Table 4. All sites were located in the U.S. except for site #8400397 which was located in Ontario, Canada (n=88).

Table 4: Study Sites, Investigators, and Number of Subjects* - CSLCT-QIV-15-03 (Full Analysis Set)**

Site	Investigator	Location	#Subjects*
8400282	William M. Seger	Fort Worth, TX	63
8400283	Laurence Chu	Austin, TX	65
8400285	Frank Steven Eder	Binghamton, NY	63
8400288	Darrell H. Herrington	San Angelo, TX	122
8400289	Mark A. Turner	Meridian, ID	51
8400308	Bernard P. Grunsta	Bristol, TN	15
8400390	Michael A. Raush	Agusta, KS	50
8400393	George Bauer, Jr.	Metairie, LA	103
8400395	Nathan G. Forbush	Layton, UT	80
8400397	Rosario B. Retino	Ontario, Canada	88
8400402	William G. Douglas	Sacramento, CA	78
8400418	Jose I. Acosta	Miami, FL	5
8400419	Donald P. Hurley	Charleston, SC	34
8400420	Renee M. Heustis	Louisville, KY	47
8400421	Robyn D. Hartvickson	Newton, KS	66
8400422	Richard H. Egelhof	Wichita, KS	72
8400423	Marilou G. Cruz	Downey, CA	31
8400424	Shane Glade Christensen	Salt Lake City, UT	67
8400425	Donald M. Brandon	San Diego, CA	43
8400426	Antonio E. Blanco	Miami, FL	20
8400427	Rogelio Amisola	Dayton, OH	72
8400428	Gary Warren Schlichter	Salt Lake City, UT	98
8400429	Robert A. Robbins	Asheboro, NC	18
8400430	Elizabeth Reyes	Anaheim, CA	66
8400431	James Todd Peterson	Salt Lake City, UT	77
8400432	Mahfouz Michael (back up site)	Los Angeles, CA	0
8400433	Judith L. Kirstein	West Jordan, UT	75
8400434	William H. Johnston	Birmingham, AL	60
8400435	Mark D. Johnson	West Jordan, UT	31
8400436	Robert J. Jeanfreau	Metairie, LA	84
8400437	Angeline Yatar-Ituriaga	Anaheim, CA	80
8400438	Paul P. Wisman, Jr.	Charlottsville, VA	68
8400439	William Travis Weathers	Spartanburg, SC	69
8400440	Randall L. Watson	West Jordan, UT	33
8400441	Jeffery L. Wampler	Louisville, KY	34
8400442	Harry Earl Studdard	Mobile, AL	72
8400443	Victoria Statler	Louisville, KY	8
8400444	Joseph A. Ley	Kingsport, TN	29
8400445	Ignatius Godoy	Paramount, CA	71
8400446	Robert W. Frenck, Jr.	Cincinnati, OH	39
Total	Total		2247

Source: Adapted from STN 125254.692, CSLCT-QIV-15-03 CSR, Appendix 16.1.4, STN 125254.692.1, Table 2, and electronic datasets.
*Number of subjects in the Full Analysis Set.
**ClinicalTrials.gov identifier: NCT02914275

6.1.7 Surveillance/Monitoring

The schedule of study procedures, including safety monitoring, is presented in Table 5.

Table 5: Schedule of Procedures – CSLCT-QIV-15-03***

Visit (V)/Phone Call	**Pre-Study**	**V1**	**Call**	**V2**	**Call****	**V3****	**Call**	**Call**
Day (D) Post Dose 1	**D -7 to -1**	**D1**	**D3+2**	**D29+4**	**--**	**--**	**D 90+7**	**D 180+7**
Day (D) Post Dose 2**	**--**	**--**	**--**	**--**	**D3+2**	**D29+4**	**D 90+7**	**D 180+7**
Assessment/ Procedure	**Screen**	**Dose1**	**Diary reminder**	**Exit*/ Dose 2****	**Diary reminder**	**Exit****	**SAE Review**	**SAE Review**
Informed consent[1]	X[1]	X[1]	--	--	--	--	--	--
Baseline characteristics[1]	X[1]	X[1]	--	--	--	--	--	--
Medical history, meds[1]	X[1]	X[1]	--	--	--	--	--	--
Weight and targeted physical exam[1]	X[1]	X[1]	--	X	--	X**	--	--
Axillary temperature	--	X	--	X**	--	--	--	--
Eligibility criteria	--	X	--	--	--	--	--	--
Serologies	--	X	--	X*	--	X**	--	--
Vaccination	--	X	--	X**	--		--	--
Provide study supplies and instructions		X		X**				
Solicited Diary review	--	--	X	X	X**	X**	--	--
Unsolicited/Concomitant Meds Diary review	--	--	X	X	X**	X**	--	--
Telephone contact	--	--	X	--	X**	--	X	X
Assess cellulitis-like reaction or ILI[2]	--	X	X	X	X**	X**	--	--
Review AEs and meds	--	X	X	X	X**	X**		
Review SAEs	--	X	X	X	X	X	X	X

Source: Adapted from Module 5, CSLCT-QIV-15-03 CSR, Tables 9.5-1 and 9.5-2, pp.76-77.
*Single dose subjects only.
**Two-dose subjects only.
***ClinicalTrials.gov identifier: NCT02914275
[1]These screening procedures could be performed on the day of or up to 7 days prior to vaccination.
[2]If applicable, assess for cellulitis-like reaction (defined as concurrent Grade 3 injection site pain, erythema, and induration) or influenza-like illness (ILI) [ILI defined as axillary temperature ≥99.5°F (≥37.5°C) or a clear history of fever or chills, and at least one respiratory symptom (including sore throat, cough, wheezing, rhinorrhea/rhinitis); and at least one systemic symptom (including myalgia, headache, malaise and fatigue, nausea and/or vomiting, diarrhea, loss of appetite, and irritability). For ILI, collect nasal swabs from right and left nares and a throat swab.

Parents or legal guardians provided written informed consent prior to any study procedures. Vaccinations were administered at Visit 1 Day 1 and, if indicated, at Visit 2 Day 29 + 4 by an unblinded study staff member who did not participate in safety assessments. Subjects were observed for immediate hypersensitivity reactions for at least 30 minutes after each vaccination.

For individual subjects eligible to receive two doses, the second vaccination was postponed in the event of clinical signs or symptoms of active infection and/or axillary temperature ≥99.5°F (≥37.5°C) within 48 hours of vaccination. Contraindications to the second vaccination included an axillary temperature of >103.1°F (39.5°C) within 48 hours of the first vaccination, assessed as related to study vaccination, or a seizure with or without fever after the first vaccination and assessed as related. Vaccination was also

postponed if a subject used a prophylactic antipyretic on the day of vaccination. Prophylactic antipyretics on the day of and seven days following vaccinations were not permitted. However, antipyretic use for the treatment of AEs, including fever, were permitted and documented as a concomitant medication.

Parents and guardians received instructions and electronic access for completing the electronic 7-Day Diary (for solicited AEs), the Other Body Symptoms Diary (for unsolicited AEs), and the Medications Diary (for all concomitant medications). Supplies included a local injection site measurement card and a digital thermometer for taking axillary temperature on the evening of vaccination and at the same time for the subsequent six days (i.e., Days 1 through Day 7). Parents and guardians received instructions to contact the investigator/delegate immediately if the subject had any signs or symptoms of severe (Grade 3) solicited or unsolicited AEs, or an influenza like-illness (ILI).

Reviewer comment: Axillary rather than oral temperatures were measured in the study because this route is more appropriate and preferred in younger children. Severity grading scales for fever were adjusted (relative to scales for older children and adults) by reducing the thresholds or cutoffs for each grade by 0.5°C or 0.9°F to account for the use of axillary rather than oral temperature. This was acceptable because axillary temperatures are approximately 0.5°C or 0.9°F lower than oral temperatures. Actual axillary temperature recordings were not altered or adjusted in the safety analyses or CSR.

In the event of a cellulitis-like reaction (concurrent Grade 3 injection site pain, erythema, and induration within 28 days of each vaccination), subjects were to return to clinic within 24 hours of onset for evaluation. Study staff assessed the injection site for ulceration, abscess, or necrosis, to determine whether halting rules were triggered.

In the event of an ILI within 28 days of any vaccination, subjects were to return to clinic within 72 hours of onset for evaluation. Criteria for ILI were:

- Elevated axillary temperature of ≥99.5°F (≥37.5°C) (or a clear history of fever or chills); AND
- At least one respiratory symptom, including sore throat, cough, wheezing, rhinorrhea/rhinitis; AND
- At least one systemic symptom, including myalgia, headache, malaise and fatigue, diarrhea, nausea and/or vomiting, loss of appetite, and irritability.

Symptoms should be new or, for chronic symptoms, changed in severity or nature.

Antiviral medications, if indicated, were not administered until after two nasal swabs (right and left nostrils) and a throat swab were collected for laboratory confirmation of influenza A/B by reverse transcriptase polymerase chain reaction (RT-PCR). These specimens could be collected up to 7 days after illness onset.

Reviewer comment: For the purposes of this study, the definition of ILI was sufficiently similar to the CDC national surveillance case definition of ILI: Temperature ≥100°F (≥37.8°C) AND cough and/or sore throat without a known cause other than influenza.

An independent DSMB, comprised of experts with experience in clinical vaccine studies and safety assessments, monitored subject safety during the trial. The DSMB was

responsible for making recommendations regarding progression of the study, described in Section 6.1.2, and reviewing safety data at regular intervals and ad hoc as necessary, including reviewing data related to halting rules if triggered.

Definitions and Criteria for the Assessment of Severity and Causality of AEs
Definitions of AEs and SAEs and reporting requirements were consistent with those in 21 CFR 312.32. AEs were followed to resolution or stabilization. Solicited AEs and the severity grading scales for both solicited and unsolicited AEs including SAEs are presented in Table 6:

Table 6: Severity Grading Scales for Adverse Events – CSLCT-QIV-15-03*

Solicited Local Reactogenicity	**Grade 0 (none)**	**Grade 1 (mild)**	**Grade 2 (moderate)**	**Grade 3 (severe)**
Pain (6-35 months)	None	Minor reaction on touch	Cries/protests on touch	Cries when limb is moved/spontaneously painful
Pain (36-59 months)	None	Does not interfere with daily activities	Interferes with daily activities	Prevents daily activity
Redness/erythema	Absent	<10 mm	≥10 mm to ≤ 30 mm	> 30 mm
Induration/swelling	Absent	<10 mm	≥10 mm to ≤ 30 mm	> 30 mm
Solicited Systemic Symptoms	**Grade 0 (none)**	**Grade 1 (mild)**	**Grade 2 (moderate)**	**Grade 3 (severe)**
Fever (axillary)[1]**	<99.5°F (<37.5°C)	≥99.5°F to <100.4°F (≥37.5°C to <38.0°C)	≥100.4°F to <101.3°F (≥38.0°C to <38.5°C)	≥101.3°F (≥38.5°C)
--Nausea and/or vomiting[1] --Diarrhea[1] --Loss of appetite[2] --Irritability[2] --Malaise/fatigue[3] --Headache[3] --Myalgia[3]	None	AE easily tolerated, causes minimal discomfort, and does not interfere with activities	AE sufficiently discomforting to interfere with daily activities	AE prevents normal everyday daily activities or requires significant medical intervention
Unsolicited Adverse Events	**Grade 0 (none)**	**Grade 1 (mild)**	**Grade 2 (moderate)**	**Grade 3 (severe)**
Event	n/a	Easily tolerated, does not interfere with normal everyday activities	Discomfort sufficient to cause some interference with normal everyday activities	Symptoms prevent normal, everyday activities

Source: Adapted from Module 5, CSLCT-QIV-15-03 CSR, Tables 9.5.3.4-1 and 9.5.3.4-2 and text p.83.
*ClinicalTrials.gov identifier: NCT02914275
**Scale adjusted (relative to scales for older children and adults) by reducing the cutoffs for each grade by 0.5°C or 0.9°F to account for the use of axillary rather than oral temperature.
[1]All subjects.
[2]Subjects 6 through 35 months only.
[3]Subjects 36 through 59 months only.
n/a=not applicable

Reviewer comment: Solicited AEs and severity grading scales were consistent with those collected in prior Seqirus and other pediatric influenza vaccine studies.

Adverse Events of Special Interest (AESIs)
The protocol and Statistical Analysis Plan (SAP) defined AESIs consistent with the Council for International Organizations of Medical Sciences (CIOMS) Working Group definition, as events potentially associated with a product or product class for which ongoing monitoring and rapid reporting are important to characterizing the safety profile

of the product. For Seqirus QIV, the Applicant's PVP has selected the following as AESIs representing either identified or potential risks associated with the pharmacologic class of influenza vaccines:

- Febrile convulsion
- Febrile delirium
- Bell's palsy
- Demyelinating disorders
- Encephalomyelitis
- Guillain-Barre syndrome
- Optic neuritis
- Transverse myelitis
- Thrombocytopenia
- Vasculitis

The Applicant considered these AESIs as medically important events worthy of reporting as SAEs. AESIs were to be recorded on the SAE page of the eCRF as meeting criteria for "medically significant" events and any other criteria as applicable.

Reviewer comment: With the exception of "febrile delirium", AESIs appear in the postmarketing section of the Afluria QIV PI as uncommon events that have been associated either with Afluria TIV or QIV or other influenza vaccines. They are monitored as part of the Afluria TIV and QIV PVP and are reported to OBE/DE and OVRR in an annual DSUR. Although they are also of interest, large/extensive injection site swelling and cellulitis-like reactions are not defined by the Applicant as AESIs but are included in the PVP as important potential risks, as recommended by OBE/DE in August 2016.

Assessment of Causality

Causality was assessed by the investigator. All solicited local AEs were considered vaccine-related. All other AEs were assessed as either related or not related to the study vaccines. If a causality assessment was not provided, the AE was considered related. Factors considered in relatedness included: known pharmacology, clinical and/or pathophysiological plausibility, similarity to events previously reported following vaccination with similar products, and temporal relationship.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoints (Immunogenicity)

Immunogenicity of the study vaccines was evaluated by measuring HI titers to each of the four virus strains included in the vaccines at 28 days following the final vaccination. The non-inferiority (NI) of Afluria QIV compared to U.S.-licensed Comparator QIV was assessed for eight co-primary endpoints of Day 28 HI geometric mean titer (GMT) ratios and seroconversion rate (SCR) differences for each of the four vaccine virus strains for the Per Protocol Population for subjects 6 through 59 months.

The GMT ratio was defined as: GMT Comparator QIV / GMT Afluria QIV.

- Success criteria for non-inferiority (NI margin): GMT ratio Comparator QIV / Afluria QIV must not exceed 1.5.

The SCR difference was defined as: SCR Comparator QIV – SCR 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 ≥1:40, or a pre-vaccination HI titer ≥1:10 and a ≥4-fold rise in post-vaccination HI titer.

- Success criteria for non-inferiority (NI margin): The SCR difference SCR Comparator QIV – SCR Afluria QIV must not exceed 10%.

Non-inferiority was established if Afluria QIV met success criteria for all eight co-primary endpoints.

Reviewer comment: Success criteria for establishing the non-inferiority of Afluria QIV relative to the comparator in this study followed FDA Guidance for Industry: Clinical Data Needed to Support Licensure of Seasonal Inactivated Influenza Vaccines, May 2007.

Secondary Endpoints (Immunogenicity)

The immunogenicity of Afluria QIV was further assessed based on serum HI antibodies pre- and 28 days after final vaccination to calculate GMT, SCR, percentage of subjects with an HI ≥1:40 (% HI ≥1:40), and geometric mean fold increase (GMFI) for each of the four vaccine virus strains in the two age strata and overall. These endpoints were also calculated according to sex, race and ethnicity.

Reviewer comment: The primary and secondary immunogenicity endpoints reflected criteria commonly used to evaluate the effectiveness of U.S.-licensed influenza vaccines. Because the GMFI is a criterion used by the European Medicines Agency (EMA) but not by CBER to assess immune responses of influenza vaccines, this review will focus only on the secondary endpoints of GMT, SCR, and % HI ≥1:40.

Secondary Endpoints (Safety)

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;
- 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.

Reviewer comment: Due to prior concerns regarding the pyrogenicity of Afluria QIV in younger age populations, the review team requested addition of an exploratory endpoint of antipyretic use during the May 11, 2016 pre-sBLA meeting with the Applicant.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Please see the statistical review for a complete discussion of the statistical analysis plan.

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. In mathematical notation, the statistical hypotheses for the primary immunogenicity analysis were:

- H0: Ri > 1.5, for any strain
- Ha: Ri ≤ 1.5, for all strains

and

- H0: Di > 10, for any strain
- Ha: Di ≤ 10, for all strains

where Ri was any of the four strain-specific Day 28 post-vaccination GMT ratios.
and Di was any of the four strain-specific Day 28 post-vaccination SCR differences.
No adjustment was made for multiple comparisons because the sample size and power were calculated based on eight co-primary endpoints. This was acceptable to the statistical reviewer and review team.

For the primary immunogenicity analyses, the GMT ratio was adjusted for the following covariates: vaccine treatment, pre-vaccination HI titer, age stratum (6-35 or 36-59 months), sex, influenza vaccination in the prior year, number of doses, and investigator site.

For safety endpoints, descriptive statistics were used to summarize the number and percentage of subjects experiencing at least one event by treatment group overall and by age stratum. Percentages and relative risk were presented with 95% CIs.
Unsolicited AEs were coded using MedDRA version 19.0

Sample Size

The sample size was calculated to provide at least 80% power to demonstrate non-inferiority for all 8 co-primary endpoints of GMT ratios and SCR differences for each of the 4 vaccine virus strains using a one-sided alpha of 0.025 for each comparison in the overall study population 6 through 59 months (therefore, no adjustment was made for multiple endpoints). NI margins of 1.5 and 10% were employed for the GMT ratio and SCR difference, respectively. Assumptions included GMT ratios of 1.0, with no difference between Afluria QIV and Comparator QIV, and a SCR of 50% for all strains, with no difference between Afluria QIV and Comparator QIV. Under these assumptions, an evaluable sample size of n=1500 for Afluria QIV and n=500 for Comparator QIV for the total study population was calculated as providing 99.95% power for the four GMT ratio endpoints and 89.70% power for the four SCR endpoints, for an overall power of 89.66% for the 8 co-primary endpoints. A total enrollment of n=2222 was planned to allow for a 10% dropout rate.

Reviewer comment: The sample size assumptions and calculations were acceptable to the review team.

Protocol Deviations and Violations

Major protocol deviations were defined as those which could significantly affect subject safety, rights, or welfare and/or significantly impact the completeness, accuracy and reliability of study data. Protocol deviations listings were reviewed by Seqirus prior to unblinding, and were used to determine which subjects should be excluded from study analysis populations. The Applicant provided a list of specific protocol deviation categories and lists of subjects found to have protocol deviations [CSR Appendix 16.1.9, SAP, Analysis Set Specification, Version 2, September 1, 2017].

Missing Data
Missing data were not imputed. HI titers <1:10 were assigned a value of 1:5 for the purpose of GMT calculations.

Subjects for whom data were missing for all 7 days for solicited AEs were omitted from the denominator when calculating the rate for those events. If severity data were only partially missing for the 7-day solicited AE period for an event, then missing severity was imputed as the maximum of the previous and next non-missing values for calculation of the aggregated value.

Interim Analysis
An interim analysis of immunogenicity and safety data collected from the active study period (Day 1 to Exit Visit, 28 days after the final vaccination) was performed to inform further clinical development.

Reviewer comment: The interim analysis represented the final immunogenicity, solicited AE, and unsolicited AE analyses. Results were communicated only to relevant personnel within Seqirus but not to personnel directly involved in monitoring the study. Seqirus Safety personnel participating in the interim analysis had no further involvement in the assessment of SAEs after the interim database lock. Study sites and Seqirus personnel interacting with study sites remained blinded until the final database lock. The review team, including the statistical reviewer, agreed that this approach was acceptable during the May 11, 2016 pre-sBLA meeting with the Applicant and review of the study protocol (IND 15974/34).

Changes in the Conduct of the Study or Planned Analyses
Minor revisions were made to the final protocol, prior to the first subject visit. Changes made to the conduct of the study or planned analyses from the final protocol were completed prior to the interim database lock (May 11, 2017) and unblinding, and included:

- Clarification that the exploratory analysis on antipyretics included concomitant medications with the following preferred names: Ibuprofen, Acetaminophen, Advil, Motrin, or Tylenol. The associated indication for these medications contained “fever” or “temperature”. If an end date was missing, the duration of these medications was computed with the Exit Visit as the end date of treatment.
- Tables for ILI and solicited local and systemic AEs overall and by maximum intensity presented CIs for relative risk (RR) using asymptotic methods rather than exact methods as originally planned. The Applicant explained that the low frequency of events would have caused the time of computation of exact CIs to be extremely extended.
- In response to an FDA request dated March 28, 2017, the Applicant added analyses of unsolicited AEs with onset from Day 1 through Day 28 following the last vaccination.

The interim clinical database was considered final and locked on May 11, 2017. On August 10, 2017, the database was unlocked to amend some data determined to be incorrect on some eCRFs. The last subject study visit was on August 11, 2017. The final database was reviewed and locked on August 30, 2017 (STN 125254/692/5).

Reviewer comment: Changes to the protocol and SAP did not break the study blind and were not likely to have introduced bias or influenced interpretation of the study results.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Analysis populations were defined as follows:

- Full Analysis Set (FAS): The FAS comprised all subjects whose parents or guardians gave informed consent and who were randomized to treatment. Screening failures were not included in the FAS but were summarized in disposition tables and listed. The FAS was used to summarize subject demographic and baseline characteristics.
- Overall Safety Population (OSP): The OSP included all randomized subjects (FAS) who received at least one dose or partial dose of study vaccine and provided any evaluable safety follow-up data.
- Solicited Safety Population (SSP): The SSP included all randomized subjects (FAS) who received at least one dose or partial dose of study vaccine and provided any evaluable data on solicited events.
- Solicited Safety Population after the First Vaccination (SSP1): The SSP1 included all randomized subjects (FAS) who received the first vaccination and provided any evaluable data on solicited AEs after the first vaccination.
- Solicited Safety Population after the Second Vaccination (SSP2): The SSP2 included all randomized subjects (FAS) who received the second vaccination and provided any evaluable data on solicited AEs after the second vaccination.
- Evaluable Population (EP): The EP included all randomized subjects in the FAS who:
    - received study vaccine at Visit 1;
    - provided valid pre- and post-vaccination serologies [at both Visit 1 and the Exit Visit (Visit 2 or 3, 28 days after the final vaccination)];
    - did not experience a laboratory-confirmed ILI between Visit 1 and the Exit Visit; and
    - did not receive a prohibited medication during the study that was medically assessed as potentially impacting immunogenicity results.
- Per Protocol Population (PPP): The PPP included all subjects in the EP who did not have any protocol deviations that were medically assessed as potentially impacting immunogenicity results. The PPP was used for the primary and secondary immunogenicity analyses.

Subjects included in the PPP and the EP were determined prior to the interim unblinding. The SAP specified that duplicate supporting analyses based on the EP would be performed if there was a > 1% difference in the total number of subjects in either of the two age strata between the PPP and EP. Because the differences in the number of subjects between the EP and the PPP were 2.38% and 3.01% for the 6-35 month and 36-59 month strata, respectively, duplicate tables of primary immunogenicity analyses were provided based on the EP.

6.1.10.1.1 Demographics

Table 7 presents demographic and baseline characteristics of the FAS according to treatment group. Distribution of characteristics across treatment groups, overall and within age cohorts (data not shown), was generally balanced. Males, whites, and non-Hispanics/Latinos comprised the majority of subjects in the overall study population (51.6%, 71.0%, and 73.1%, respectively). The mean age (SD) of all subjects was 36.6 (14.69) months; 21.7 (8.59) for the 6-35 month age cohort; and 47.1 (6.94) for the 36-59 months age cohort. As specified by the protocol, no more than 60% of all subjects in the FAS were enrolled in either age cohort (6-35 months 41.6%; 36-59 months 58.4%).

Table 7: Demographic and Baseline Characteristics – CSLCT-QIV-15-03 (Full Analysis Set)*

Characteristic	Afluria QIV N=1684	Comparator QIV N=563	Total N=2247	U.S. Census (2015)**
Mean Age (months) (SD)	36.6 (14.70)	36.5 (14.68)	36.6 (14.69)	--
Age Group %	--	--	--	--
6-35 mos	41.6	41.7	41.6	--
36-59 mos	58.4	58.3	58.4	--
Gender – Male, %	51.3	52.4	51.6	49.3
Gender – Female, %	48.7	47.6	48.4	50.7
Race, %	--	--	--	--
American Indian/Alaska Native	0.3	0.4	0.3	1.2
Asian	0.9	1.8	1.1	5.5
Black/African American	21.4	21.8	21.5	13.2
Native Hawaiian/Pacific Islander	0.8	0.5	0.7	0.2
White/Caucasian	71.6	69.4	71.0	77.3
Other	5.0	6.0	5.3	--
Ethnicity, %	--	--	--	--
Hispanic/Latino	25.8	28.4	26.4	17.7
Non-Hispanic/Latino	73.8	71.0	73.1	82.3
Not reported/Unknown	0.5	0.5	0.4	--

Source: Adapted from STN 125254/692, Module 5, CSLCT-QIV-15-03 CSR, Tables 11.2-1, 14.1.2.1, and 14.1.2.2
*ClinicalTrials.gov identifier: NCT02914275
**Population projections for 2015 released by the U.S. Census Bureau in December 2014 based on the 2010 U.S. Census. Accessed on November 29, 2017 at https://www.census.gov/data/tables/2014/demo/popproj/2014-summary-tables.html
Estimated total U.S. population=321,369,000. Male=158,345,000 (49.3%). Female=163,024,000 (50.7%). White=248,369,000. Black/African American=42,456,000. American Indian/Alaskan Native=4,005,000. Asian=17,538,000. Native Hawaiian/Pacific Islander=746,000. ≥two races=8,225,000. Non-Hispanic/Latino=264,615,000. Hispanic/Latino=56,754,000. Estimated persons <5 years=19,965,000. Males <5 years=10,211,000 (51.1%). Females <5 years=9,755,000 (48.9%).

Reviewer comment: Differences in demographic and baseline characteristics were small between treatment groups and were not likely to impact interpretation of study results. Relative to the total U.S. population, blacks/African Americans and Hispanics/Latinos were overrepresented, and Asians were underrepresented. However, because census data for race and ethnicity were not available for the pediatric population 6-59 months, the reviewer is not certain that percentages for the total U.S. population are representative of U.S. children 6-59 months. [75]

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Influenza Vaccination History

Of the 2247 subjects in the FAS, 1662 (74%) subjects reported ever having received an influenza vaccine including 50.7% in the 2015-2016 NH season during the 12 months

prior to enrollment. The percentages of subjects who reported ever receiving influenza vaccination were lower in children 6-35 months as compared to 36-59 months of age (56.7% and 86.3%, respectively), but similar for the previous NH 2015-2016 season (50.4% and 50.9%, respectively). The percentages of subjects 6-59 months who reported ever receiving influenza vaccination differed only slightly between treatment groups (Afluria QIV 73.3%, Comparator QIV 76.0%).

Based on prior vaccination history, a total of 38.7% and 40.2% of subjects randomized to the Comparator QIV and Seqirus QIV groups, respectively, or 39.8% of subjects overall, were eligible for two doses of study vaccine.

Medical History

The most common pre-existing conditions among all subjects in the FAS (≥10%), categorized by MedDRA system organ class (SOC), were immune system disorders (13.2%) and infections and infestations (12.4%). Immune system disorders included seasonal allergies (10.1%), drug hypersensitivity (2.6%), and various other allergies (≤0.8%). Infections and infestations included otitis media (4.6%), upper respiratory tract infection (3.1%), and various other infections (≤0.9%). Overall, similar proportions of subjects in each treatment group reported having pre-existing medical conditions. A history of febrile convulsions was reported by 0.1% of subjects in the 6-35 months age stratum [Afluria QIV n=1 (0.1%), Comparator QIV n=0] and by 0.3% of subjects in the 36-59 months age stratum [Afluria QIV n=3 (0.3%), Comparator QIV n=1 (0.3%)]. No subjects reported having immunosuppressive conditions at baseline, including significant malignancies or diabetes.

Concomitant Medications

A total of 38.9% of subjects in the FAS (42.1% of subjects 6-35 months and 36.5% of subjects 36-59 months) reported taking concomitant medications during the study. Similar proportions of subjects between treatment groups overall and within each age stratum reported using anti-pyretic medications and inhaled or topical corticosteroids. Subject #(b) (6) (Afluria QIV, 36-59 months age group) received Fluarix influenza vaccine (a prohibited medication) twelve days post-vaccination and was excluded from immunogenicity analyses. Subject #(b) (6) (Afluria QIV, 36-59 months age group) received oseltamivir, 45 mg orally twice daily for five days beginning 31 days post-vaccination (after collection of post-vaccination serologies), as "prophylaxis", and completed the study. The subject had no reported unsolicited AEs or documented ILI, and was included in the PPP and SP. Please see Section 6.1.12.2 for results of the exploratory analysis of the frequency of antipyretic use in the seven days following vaccinations.

Reviewer comment: Concomitant medication use was similar between treatment groups. Evaluation of the CSR and electronic datasets indicated that 26 (1.5%) Afluria QIV recipients and 6 (1.1%) Comparator QIV recipients in the FAS received systemic corticosteroids (primarily oral) during the study, for acute respiratory conditions such as croup, bronchitis, bronchiolitis, community-acquired pneumonia, wheezing, and exacerbation of asthma. No other potentially immunosuppressive agents were reported as being used by subjects during the study. Overall, influenza vaccination history, medical history, and concomitant medications were balanced between treatment groups.

6.1.10.1.3 Subject Disposition

Table 8 presents the disposition of subjects and analysis populations.

Table 8: Subject Disposition and Analysis Populations (All Subjects) – CSLCT-QIV-15-03*

Population*	**Afluria QIV N (%)****	**Comparator QIV N (%)****	**Total N (%)****
Screened, n	--	--	2339
Screening failures, n	--	--	89
Randomized, n	1687	563	2250
Randomized in error, not vaccinated, n	3	0	3
Full Analysis Set (FAS), n(%)	1684 (100)	563 (100)	2247 (100)
Discontinued before vaccination, n	5	2	7
Vaccinated but provided no safety data, n	6	2	8
Overall Safety Population, n(%)	1673 (99.3)	559 (99.3)	2232 (99.3)
Solicited Safety Population, n(%)	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, n(%)[1,3]	1492 (88.6)	503 (89.3)	1995 (88.8)
Per Protocol Population, n(%)[2,3]	1456 (86.5)	484 (86.0)	1940 (86.3)
Completed study, n(%)	1566 (93.0)	521 (92.5)	2087 (92.9)
Discontinued from study, n(%)	118 (7.0)	42 (7.5)	160 (7.1)
Adverse event, n	0	0	0
Death, n	0	0	0
Lost to follow-up, n(%)	84 (5.0)	29 (5.2)	113 (5.0)
Other, n(%)[4]	4 (0.2)	1 (0.2)	5 0.2)
Investigator decision, n(%)	3 (0.2)	1 (0.2)	4 (0.2)
Major protocol deviation, n(%)	1 (0.1)	1 (0.2)	2 (0.1)
Withdrawal by subject, n	26 (1.5)	10 (1.8)	36 (1.6)

Source: Adapted from STN 125254/692, Module 5, CSLCT-QIV-15-03 CSR, Tables 14.1.1.1 and 14.1.5.1, Figures 10.1-1 and 10.1-2, text pp.105-118, Appendix 16.1.9, and electronic datasets.
*ClinicalTrials.gov identifier: NCT02914275
**Percentages based on number of subjects in Full Analysis Set (FAS) in each group.
[1]The Evaluable Population (EP) excluded 252 subjects in the FAS who had one or more of the following violations: withdrew before vaccination (n=7); did not have valid pre- and post-vaccination serologies (n=218); received prohibited medications (n=29); and/or had an influenza-like illness between Visit 1 and Exit Visit but laboratory confirmation specimens were missing (n=9).
[2]The Per Protocol Population (PPP) excluded 55 subjects in the EP (total n=307 excluded from FAS) who had one or more protocol deviations medically assessed as potentially impacting immunogenicity results: violated age-related inclusion criteria (n=7); violated good health inclusion criterion (n=1); violated signs of active infection/fever exclusion criterion (n=34); allocated to wrong dosing regimen (n=5); post-vaccination serology drawn >49 days after the final vaccination (n=13); received only one of two doses (n=2).
[3]The final SAP Analysis Set Specifications indicates that two subjects had insufficient blood drawn to allow testing of all 4 antigens tested at both Visit 1 and the Exit Visit (Visit 2 or 3). For subject (b) (6), serologies were not performed on Day 1 for the B/Victoria antigen. For subject (b) (6), serologies were not performed at the Exit Visit for the A/H3N2 antigen. These two subjects were included in the EP and the PPP.
[4]Other reasons for discontinuation from the study included non-compliance with study visits (n=1), death of mother (n=2), parental custody issue (n=1), and phlebotomy "too traumatic" (n=1).

Subject disposition for the two age cohorts was generally similar to the overall study population. Relatively more subjects 6-35 months discontinued the study as compared to subjects 36-59 months (8.8% vs 5.9%), primarily because they were lost to follow-up. Table 9 presents analysis populations by age cohort.

Table 9: Subject Disposition and Analysis Populations by Age Group (Full Analysis Set) – CSLCT-QIV-15-03*

Age Group	6-35 mos	6-35 mos	6-35 mos	36-59 mos	36-59 mos	36-59 mos
Population, n(%)**	**Afluria QIV N(%)**	**Comparator QIV N(%)**	**Total N(%)**	**Afluria QIV N(%)**	**Comparator QIV N(%)**	**Total N(%)**
Full Analysis Set	700 (100)	235 (100)	935 (100)	984 (100)	328 (100)	1312 (100)
Overall Safety Population	694 (99.1)	233 (99.1)	927 (99.1)	979 (99.5)	326 (99.4)	1305 (99.5)
Solicited Safety Population	669 (95.6)	227 (96.6)	896 (95.8)	949 (96.4)	318 (97.0)	1267 (96.3)
Solicited Safety 1	663 (94.7)	227 (96.6)	890 (95.2)	946 (96.1)	317 (96.6)	1263 (96.3)
Solicited Safety 2	350 (50.0)	119 (50.6)	469 (50.2)	201 (20.4)	66 (20.1)	267 (20.4)
Evaluable Population	597 (85.3)	201 (85.5)	798 (85.3)	895 (91.0)	302 (92.1)	1197 (91.2)
Per Protocol Population	586 (83.7)	193 (82.1)	779 (83.3)	870 (88.4)	291 (88.7)	1161 (88.5)
Completed Study	640 (91.4)	213 (90.6)	853 (91.2)	926 (94.1)	308 (93.9)	1234 (94.1)
Discontinued Study	60 (8.6)	22 (9.4)	82 (8.8)	58 (5.9)	20 (6.1)	78 (5.9)
Adverse event	0	0	0	0	0	0
Lost to follow-up	43 (6.1)	15 (6.4)	58 (6.2)	41 (4.2)	14 (4.3)	55 (4.2)
Other	0	0	0	4 (0.4)	1 (0.3)	5 (0.4)
Investigator decision	0	1 (0.4)	1 (0.1)	3 (0.3)	0	3 (0.2)
Major protocol deviation	0	1 (0.4)	1 (0.1)	1 (0.1)	0	1 (0.1)
Withdrawal by subject	17 (2.4)	5 (2.1)	22 (2.4)	9 (0.9)	5 (1.5)	14 (1.1)

Source: STN 125254/692, Module 5, CSLCT-QIV-15-03 CSR, Table 14.1.1.2, and electronic datasets.
*ClinicalTrials.gov identifier: NCT02914275
**Percentages based on number of subjects in Full Analysis Set (FAS) in each group.
Solicited Safety 1 = Solicited Safety Population after the first vaccination
Solicited Safety 2 = Solicited Safety Population after the second vaccination

Reviewer comment: Evaluation of the electronic datasets confirmed the Applicant's report of subject disposition. Overall, 7.1% of subjects discontinued the study, most were lost to follow-up (5.0%), none were due to AEs. The dropout/discontinuation rates were relatively low, similar across treatment groups, and were unlikely to have significantly impacted the interpretation of immunogenicity or safety results.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The immunogenicity of each study vaccine was assessed 28 days after the final vaccination by measuring HI antibody titers to the four virus strains included in the vaccines. Table 10 presents results of post-vaccination HI GMTs, SCRs, and analyses of NI for adjusted GMT ratios and SCR differences for each vaccine virus strain in the Per Protocol Population 6 through 59 months.

Table 10: 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 (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 both NI Criteria?[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

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 both NI Criteria?[5]
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
[1]GMTs adjusted for covariates: vaccine treatment, age stratum, sex, pre-vaccination GMT, influenza vaccination in the prior year, number of doses, and investigator site.
[2]GMT ratio=Comparator QIV / Afluria QIV.
[3]SCR 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.
[4]SCR difference=Comparator QIV SCR minus Afluria QIV SCR.
[5]Non-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%.
[6]Subject (b) (6) was excluded from the PPP for the adjusted GMT analysis for the GMT ratio due to unknown previous vaccination history.
[7]Subject (b) (6) had missing A/H3N2 post-vaccination titer.
[8]Subject (b) (6) had missing B/Victoria pre-vaccination titer.

Reviewer comment: Afluria QIV met the eight pre-specified co-primary endpoints required to demonstrate NI to a U.S.-licensed comparator QIV in children 6 through 59 months. GMTs and GMT ratios calculated from unadjusted GMTs were similar to GMTs and GMT ratios adjusted for covariates and also met NI criteria (see CSLCT-QIV-15-03 CSR Table 14.2.1.1).

Reviewer comment: Results of the primary NI analyses based on the EP were very similar to those based on the PPP (see CSLCT-QIV-15-03 CSR Tables 14.2.1.2 and 14.2.2.2).

Reviewer comment: Immune responses elicited by both study vaccines against the B virus strains were much lower than responses to the A virus strains. A pattern of lower responses to the B strain has been observed in previous immunogenicity studies of Afluria (TIV and QIV) and other inactivated influenza vaccines, and may reflect lower rates of prior wild type or vaccine exposure to influenza B antigens as compared to A subtypes.

6.1.11.2 Analyses of Secondary Endpoints

Descriptive analyses of secondary endpoints included the calculation of pre- and post-vaccination GMTs, the percentage of subjects with post-vaccination HI titers ≥1:40, and SCRs. Secondary endpoints were summarized for the overall PPP, and by age strata, sex, race and ethnicity. Some of these data are presented in the tabular summary of the primary analyses of non-inferiority (point estimates for GMTs and SCRs, Table 10 in Section 6.1.11.1), and are summarized only briefly in this section. (Detailed results of these analyses are located in Tables 11.4-2, 11.4-3, 14.2.1.1, 14.2.2.1, 14.2.3.1,

14.2.3.2, 14.2.5.1, and 14.2.5.2 of the CSR for CSLCT-QIV-15-03, STN 125254/692, Module 5).

- Pre-vaccination (Day 1) GMTs for each of the four vaccine virus strains were similar between treatment groups within each age cohort. Pre-vaccination GMTs to the A virus strains tended to be higher in the 36-59 months (point estimates ranging 60.7-68.7) than the 6-35 months age cohort (point estimates ranging 13.8-16.4), while pre-vaccination GMTs to the B virus strains were similar between young and older age groups (point estimates ranging 5.8-7.1 and 7.9-10.4, respectively). For recipients of Afluria QIV, post-vaccination unadjusted GMT point estimates for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria were higher in subjects 36-59 months (590.2, 778.6, 35.4, and 72.1, respectively) as compared to subjects 6-35 months (184.9, 184.9, 15.6, and 39.8, respectively). Responses to B virus strains, especially to B/Yamagata, were lower than to A virus strains in both age groups. Post-vaccination GMTs were similar between treatment groups in the 6-35 months age group. For subjects 36-59 months, post-vaccination GMTs in Afluria QIV recipients, as compared to Comparator QIV, showed a higher trend for the A/H1N1 strain (590.2 vs 469.2) and a lower trend for A/H3N2 (778.6 vs 1047), B/Yamagata (35.4 vs 44.1), and B/Victoria (Afluria QIV 72.1, Comparator QIV 85.9).
- Within each age stratum and overall, pre-vaccination percentages of subjects with HI titers of ≥1:40 (% HI ≥1:40) were similar between treatment groups and were higher against A virus strains than B strains. Pre-vaccination HI titers against all virus strains were higher in the 36-59 months age group than the 6-35 months group. Post-vaccination % HI ≥1:40 were similar between age and treatment groups for both the A/H1N1 and A/H3N2 strains. Post-vaccination % HI ≥1:40 were lower for the B virus strains as compared to the A strains, especially for B/Yamagata. Post-vaccination % HI ≥1:40 for both B virus strains were higher for the 36-59 months age group as compared to 6-35 months, but were similar between treatment groups within each age cohort. In recipients of Afluria QIV, the LBs on the two-sided 95% CI for the percentages of subjects with a post-vaccination HI titer ≥1:40 for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria in children 6-35 months were 87.4%, 90.0%, 21.3%, and 51.5%, respectively. The LBs on the two-sided 95% CI for the % HI ≥1:40 in children 36-59 months who received Afluria QIV were 98.2%, 97.3%, 53.8%, and 67.9%, respectively. The LBs on the two-sided 95% CI for the % HI ≥1:40 in children 6-59 months who received Afluria QIV were 94.3%, 94.9%, 41.5% and 62.3%, respectively.
- Seroconversion rates were similar between treatment groups within each age cohort, were lower for A virus strains than B strains, and lowest for B/Yamagata. The LBs of the two-sided 95% CI for SCRs to Afluria QIV for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria were 78.6%, 79.1%, 19.2%, and 48.8%, respectively, in children 6-35 months; 74.2%, 79.5%, 46.5%, and 61.8%, respectively, in children 36-59 months; and 76.9%, 80.2%, 36.4%, and 57.6% in children 6-59 months.

Reviewer comment: A secondary objective of the study was to further characterize the immunogenicity of Afluria QIV in the two age strata and overall. For the A/H1N1 and A/H3N2 virus antigens, Afluria QIV met immune response criteria commonly used to evaluate influenza vaccines, i.e., that the LB of the 95% CI for the post-vaccination % HI titer ≥1:40 is at least 70% and the SCR is at least 40%, in subjects 6 through 59 months, overall and within each age cohort.

Immune responses to the B virus strains were notably lower in both age cohorts, especially in subjects 6 through 35 months and for the B/Yamagata antigen. Afluria QIV met immune response criteria only for the SCR for B/Victoria in the younger age cohort, and met criteria for the SCRs but not for the % HI ≥1:40 for either of the B strains in the older age cohort. Immune responses in subjects who received Comparator QIV followed the same pattern.

Reviewer comment: Lower pre- and post-vaccination HI GMTs, SCRs, and proportions of subjects with HI ≥1:40 against the B virus strains may reflect lower rates of prior wild type or vaccine exposure to influenza B antigens as compared to A subtypes. A pattern of lower responses to B strains is not unusual for influenza vaccines and, as presented in Section 6.1.11.1, Afluria QIV demonstrated non-inferior immunogenicity relative to the comparator.

6.1.11.3 Subpopulation Analyses

Subpopulation analyses conducted by sex, race and ethnicity were pre-specified secondary descriptive analyses and were not powered for statistical hypothesis testing.

Sex

Males and females comprised 51.5% and 48.5% of the PPP, respectively. Post-vaccination GMTs, % HI ≥1:40, and SCRs were similar between sexes in each treatment group. Table 11 summarizes immune responses to each vaccine strain for Afluria QIV recipients according to sex.

Table 11: Post-vaccination GMT, % HI ≥1:40, and SCR in Afluria QIV Recipients according to Sex (Per Protocol Population)* – CSLCT-QIV-15-03**

Endpoint	GMT (95% CI)	GMT (95% CI)	%HI ≥1:40 LB 95% CI	%HI ≥1:40 LB 95% CI	SCR LB 95% CI	SCR LB 95% CI
Strain	**Male N=736**	**Female N=720**	**Male N=736**	**Female N=720**	**Male N=736**	**Female N=720**
A/H1N1	349.1 (315,386)	392.6 (357,431)	92.8%	94.6%	74.8%	77.0%
A/H3N2	438.7 (391,492)	434.7 (389,486)	93.3%	95.4%	79.1%	79.5%
B/Yamagata	25.7 (24,28)	25.2 (23,27)	41.7%	39.1%	36.4%	34.2%
B/Victoria	56.9 (52,63)	56.6 (51,63)	61.4%	61.1%	56.0%	57.0%

Source: STN 125254/692, Module 5, CSLCT-QIV-15-03 CSR, Tables 14.2.3.3 and 14.2.5.3.
Abbreviations: GMT=geometric mean titer; HI=hemagglutination inhibition; %HI ≥1:40=percentage of subjects with post-vaccination HI titer of at least 1:40; SCR=seroconversion rate; LB 95% CI=lower bound of the 95% confidence interval.
*Afluria recipients in PPP subgroups: Male, n=736 (50.5%); Female, n=720 (49.5%)
**ClinicalTrials.gov identifier: NCT02914275

Reviewer comment: Immune responses between male and female recipients of Afluria QIV were similar.

Race

The majority of subjects in the PPP were white (n=1405, 72.4%). Black/African American subjects comprised 20.7% (n=402) of the PPP while other identified racial groups each comprised ≤1%. Descriptive sub-analyses of GMTs, post-vaccination % HI ≥1:40, and SCRs were conducted for white and black races. Small sample sizes

precluded meaningful sub-analyses of other racial groups. Table 12 summarizes immune responses to each vaccine strain for Afluria QIV recipients according to race.

Table 12: Post-vaccination GMT, % HI ≥1:40, and SCR in Afluria QIV Recipients according to Race (Per Protocol Population)* – CSLCT-QIV-15-03**

Endpoint	GMT (95% CI)	GMT (95% CI)	%HI ≥1:40 LB 95% CI	%HI ≥1:40 LB 95% CI	SCR LB 95% CI	SCR LB 95% CI
Strain	**White N=1062**	**Black N=302**	**White N=1062**	**Black N=302**	**White N=1062**	**Black N=302**
A/H1N1	330.8 (305,359)	513.0 (443,594)	93.0%	95.7%	75.9%	74.5%
A/H3N2	397.2 (361,437)	542.5 (459,641)	93.8%	95.7%	79.1%	80.2%
B/Yamagata	23.8 (22,26)	30.2 (26,34)	38.3%	44.2%	33.4%	38.4%
B/Victoria	56.1 (52,61)	57.5 (50,66)	59.7%	66.1%	54.9%	61.6%

Source: STN 125254/692, Module 5, CSLCT-QIV-15-03 CSR, Tables 14.2.3.4 and 14.2.5.4.
Abbreviations: GMT=geometric mean titer; HI=hemagglutination inhibition; %HI ≥1:40=percentage of subjects with post-vaccination HI titer of at least 1:40; SCR=seroconversion rate; LB 95% CI=lower bound of the 95% confidence interval.
*Afluria recipients in PPP subgroups: White, n=1062 (72.9%); Black, n=302 (20.7%)
**ClinicalTrials.gov identifier: NCT02914275

Post-vaccination (28 days after the last vaccination) GMTs in blacks/African American recipients of Afluria QIV tended to be higher (non-overlapping 95% CIs) as compared to whites for the A/H1N1 and A/H3N2 strains included in the vaccines. However, post-vaccination GMTs for the B strains and post-vaccination % HI ≥1:40 and SCRs for all four vaccine virus strains were generally similar between the two racial subgroups.

Ethnicity

The majority of all subjects in the PPP were non-Hispanic/Latino (n=1435, 74.0%). Hispanic/Latino subjects comprised 25.5% (n=495) of the PPP. Table 13 summarizes immune responses to each vaccine strain for Afluria QIV recipients according to ethnicity.

Table 13: Post-vaccination GMT, % HI ≥1:40, and SCR in Afluria QIV Recipients according to Ethnicity (Per Protocol Population)* – CSLCT-QIV-15-03**

Endpoint	GMT	GMT	%HI ≥1:40 LB 95% CI	%HI ≥1:40 LB 95% CI	SCR LB 95% CI	SCR LB 95% CI
Strain	**Non-Hispanic/ Latino N=1090**	**Hispanic/ Latino N=359**	**Non-Hispanic/ Latino N=1090**	**Hispanic/ Latino N=359**	**Non-Hispanic/ Latino N=1090**	**Hispanic/ Latino N=359**
A/H1N1	373.4 (345,404)	362.6 (315,418)	94.5%	91.5%	76.9%	73.3%
A/H3N2	425.2 (388,466)	474.7 (402,561)	95.0%	92.5%	81.0%	74.8%
B/Yamagata	25.4 (24,27)	25.2 (22,28)	40.9%	39.1%	35.9%	33.4%
B/Victoria	56.8 (52,62)	56.2 (48,66)	63.4%	55.2%	58.4%	51.2%

Source: STN 125254/692, Module 5, CSLCT-QIV-15-03 CSR, Tables 14.2.3.5 and 14.2.5.5.
Abbreviations: GMT=geometric mean titer; HI=hemagglutination inhibition; %HI ≥1:40=percentage of subjects with post-vaccination HI titer of at least 1:40; SCR=seroconversion rate; LB 95% CI=lower bound of the 95% confidence interval.
*Afluria recipients in PPP: Non-Hispanic/Latino, n=1090 (74.9%); Hispanic/Latino, n=359 (24.7%)
**ClinicalTrials.gov identifier: NCT02914275

Post-vaccination GMTs, % HI ≥1:40, and SCRs in Hispanic/Latino recipients of Afluria QIV were generally similar to non-Hispanic/Latinos for the four vaccine strains. SCRs for the A/H3N2 and B/Victoria antigens were lower in Hispanic/Latino recipients than in non-Hispanic/Latino recipients of Afluria QIV.

Reviewer comment: Overall, subanalyses of immune responses by sex, race and ethnicity followed patterns observed in the overall Per Protocol Population, and were generally similar between subgroups and treatment groups (data not shown for Comparator QIV subgroups). Descriptive subgroup analyses showed a trend towards higher post-vaccination GMTs for the A/H1N1 and A/H3N2 antigens in black as compared to white recipients of Afluria QIV. The clinical significance of these observations is unknown, and results are limited by the relatively small sample sizes and descriptive nature of the analyses. Very small sample sizes precluded meaningful analyses of other racial subgroups.

6.1.11.4 Dropouts and/or Discontinuations

Please see Sections 6.1.9, Statistical Considerations and Statistical Analysis Plan, and 6.1.10.1.3, Subject Disposition. Dropouts were not replaced and missing data were not imputed. Overall, 7.1% of subjects discontinued the study, mostly due to lost to follow-up (5.0%). Discontinuation rates were similar between treatment groups and were unlikely to introduce bias or impact interpretation of immunogenicity results.

6.1.11.5 Exploratory and Post Hoc Analyses

Influenza-like Illness

ILI's were not actively collected in the study, however, subjects were instructed to report flu-like symptoms and return to clinic for an ILI evaluation that included nasal swabs for influenza PCR (please see Section 6.1.7). A total of 85 (3.8%) of subjects in the FAS [62 of 1684 (3.7%) Afluria QIV recipients and 23 of 563 (4.1%) Comparator QIV recipients] reported having an ILI. None of these subjects had a positive laboratory confirmation between the first vaccination and the Exit Visit (28 +4 days after the final vaccination).

6.1.12 Safety Analyses

6.1.12.1 Methods

The Overall Safety Population (OSP), all randomized subjects (FAS) who received at least one dose or partial dose of study vaccine and provided any evaluable safety follow-up data, was used to summarize all safety data. The OSP was comprised of 2,232 subjects, including 1673 and 559 who were vaccinated with Afluria QIV and Comparator QIV, respectively. Data were analyzed according to actual treatment received. The Solicited Safety Population (SSP) included all randomized subjects (FAS) who received at least one dose or partial dose of study vaccine and provided any evaluable data on solicited events. Solicited AEs were actively collected via an electronic diary for seven days following each vaccination. The SSP was sub-divided into populations exposed to the first and second vaccinations (SSP1 and SSP2, respectively) as described in Section 6.1.10.1. Analyses of Solicited AEs following any vaccination are presented for the SSP according to age stratum due to collection of different solicited systemic AEs in each age stratum and a theoretical potential for higher rates of febrile events with decreasing age as had been observed in previous studies of Afluria TIV. Solicited AEs following the first

and second vaccinations are also summarized. The OSP was used to summarize unsolicited AEs and SAEs, overall and by age stratum. Unsolicited AEs and cellulitis-like reactions were passively collected for 28 days and SAEs for six months post-vaccination via a second electronic diary as outlined in Section 6.1.7.

6.1.12.2 Overview of Adverse Events

Table 14summarizes all solicited and unsolicited AEs reported in CSLCT-QIV-15-03 according to treatment group and overall.

Reviewer comment: All solicited local AEs were considered related to the study vaccines and, therefore, may also be called adverse reactions (ARs). Solicited systemic AEs do not always represent reactogenicity to study vaccine and, in randomized placebo-controlled trials, the frequency of these events in recipients of the investigational product may be similar to placebo recipients. Solicited systemic AEs in this study were assessed for relatedness by the investigator and are termed adverse events.

Table 14: Summary of All Solicited and Unsolicited Adverse Events through Day 28 including Serious Adverse Events through Day 180 (Overall Safety Population)* – CSLCT-QIV-15-03**

Parameter	Afluria QIV N=1673 (%)*	Comparator QIV N=559 (%)*	Overall N=2232 (%)*
One or more Adverse Events (AE)[1]	65.0	65.8	65.2
Maximum Intensity[2]			
• Grade 1	35.1	35.1	35.1
• Grade 2	23.4	22.0	23.1
• Grade 3	6.4	8.6	6.9
One or more related AEs	53.0	53.3	53.0
Discontinuations due to AE	0	0	0
Solicited Adverse Events – Any[3]	58.1	57.2	57.9
Maximum Intensity[2]			
• Grade 1	36.6	34.7	36.1
• Grade 2	17.1	15.2	16.6
• Grade 3	4.4	7.2	5.1
• Missing	0	0.2	<0.1
Solicited Local Adverse Reactions[4]	39.9	38.2	39.4
• Cellulitis-like reaction through Day 28	0	0.2	<0.1
Solicited Systemic Adverse Events	39.1	39.4	39.2
• Related solicited systemic AEs[5]	29.4	30.5	29.6
Unsolicited Adverse Events – Any[6]	32.0	30.6	31.7
Maximum Intensity[1]			
• Grade 1	17.0	16.5	16.9
• Grade 2	12.3	11.6	12.1
• Grade 3	2.7	2.5	2.6
• Missing	0	0	0
Related Unsolicited AEs[4]	8.5	9.3	8.7
SAEs through Day 28	0.2	0	0.2
SAEs from Day 29 through Day 180	0.4	0.5	0.4
Related SAEs through Day 180[5]	0	0	0
Discontinuations due to SAEs through Day 180	0	0	0
Deaths through Day 180	0	0	0
AESIs through Day 28	0	0	0
AESIs from Day 29 to Day 180	0.1	0	0.1

Source: Adapted from STN 125254/692, Module 5, CSLCT-QIV-15-03 CSR Tables 12.2.1-1, 14.3.1.1.1.1 and 14.3.1.1.1.2.
Abbreviations: QIV=quadrivalent influenza vaccine; SAE=serious adverse event; AESI=adverse event of special interest.

*Percentage based on number of subjects in each group. Denominators are based on the Overall Safety Population except for solicited AEs which are based on Solicited Safety Population.
**ClinicalTrials.gov identifier: NCT02914275.
[1]Any solicited AE through 7 days after any vaccination, cellulitis-like reaction through 28 days after any vaccination, or unsolicited AE, regardless of seriousness, through 28 days after any vaccination; .
[2]Subjects were counted only once for multiple events of the same intensity
[3]Any solicited AE through 7 days after any vaccination or cellulitis-like reaction through 28 days after vaccination. Solicited Safety Population: Afluria QIV=1618; Comparator QIV=545; Overall=2163
[4]All solicited local adverse reactions were considered related to study vaccine.
[5]Relatedness as assessed by the Investigator.
[6]Any unsolicited AE, regardless of seriousness, through 28 days following any vaccination.

Reviewer comment: In the 28 days following any vaccination, proportions of AEs between Afluria QIV and Comparator QIV were similar overall, 65.0% vs 65.8%, respectively, both for solicited AEs (58.1% vs 57.2%, respectively) and unsolicited AEs (32.0% vs 30.6%, respectively). Rates of SAEs were low and similar between Afluria QIV and Comparator QIV, both in the 28 days following any vaccination (0.2% vs 0, respectively) and from Day 29 through Day 180 (0.4% vs 0.5%, respectively). No subjects died or were discontinued due to AEs during the study.

Reviewer comment: Evaluation of the electronic datasets yielded numbers and rates of solicited and unsolicited AEs, and rates of severity of AEs, identical to the Applicant's report.

Solicited Local Adverse Reactions – Subjects 6 through 35 Months

Table 15 summarizes the rates of solicited local ARs reported in the seven days following vaccination (Day 1 through Day 7) in subjects 6-35 months according to dose, treatment, and maximum severity.

Table 15: Solicited Local Adverse Reactions by Dose and Maximum Severity, Subjects 6 through 35 Months (Solicited Safety Population)* – CSLCT-QIV-15-03**

--	Local AR	Afluria N=669	Afluria N=669	Afluria N=669	Afluria N=669	Comp N=227	Comp N=227	Comp N=227	Comp N=227	Overall N=896
Dose	Reaction	Mild %[1]	Mod %[1]	Sev %[1]	All %[1]	Mild %[1]	Mod %[1]	Sev %[1]	All %[1]	All %[1]
Any	Any	23.7	8.4	0.7	32.9	23.5	8.0	2.7	34.4	33.3
Any	Pain	15.2	5.4	0.1	20.8	19.8	5.3	0.4	25.6	22.0
Any	Swelling	4.5	1.2	0.4	6.1	4.4	0.9	0.9	6.2	6.1
Any	Redness	16.6	3.4	0.6	20.8	13.7	1.8	1.8	17.6	20.0
1st	Any	22.5	6.9	0.6	30.0	21.7	7.1	2.7	31.7	30.4
1st	Pain	13.6	4.4	0	17.9	18.9	4.8	0.4	23.3	19.3
1st	Swelling	3.9	1.1	0.5	5.4	3.5	0.9	0.9	5.3	5.4
1st	Redness	15.7	3.0	0.6	19.3	11.1	1.3	1.8	14.5	18.1
2nd	Any	14.9	3.7	0.3	19.1	16.8	2.5	0	19.3	19.2
2nd	Pain	9.7	2.6	0.3	12.6	10.9	1.7	0	12.6	12.6
2nd	Swelling	2.3	0.3	0	2.6	4.2	0	0	4.2	3.0
2nd	Redness	8.9	0.9	0	10.0	10.1	0.8	0	10.9	10.2

Source: STN 125254.692, Module 5, CSLCT-QIV-15-03 CSR, Tables 12.2.2-1, 14.3.1.2.2, 14.3.1.2.5, and 14.3.1.2.6.
*Abbreviations and Populations: AR=adverse reaction; Afluria=Afluria QIV; Comp=Comparator QIV; Mild=Grade 1; Mod=Moderate (Grade 2); Sev=Severe (Grade 3); All=All subjects with a specific local reaction; Any reaction=subjects with any local reaction after any vaccination (based on the Solicited Safety Population after any vaccination, SSP); 1st=subjects with local reaction after first vaccination (based on the Solicited Safety Population after Dose 1, SSP-1); 2nd=subjects with local reaction after second vaccination (based on the Solicited Safety Population after Dose 2, SSP-2).
**ClinicalTrials.gov identifier: NCT02914275

[1]Denominators for percentages based on # of subjects with non-missing data for each population, each group, and each parameter. For the SSP, # of subjects with non-missing data for any local AR and redness: Afluria QIV n=668; Comparator QIV n=226; Overall n=894; and for pain and swelling: Afluria QIV n=669; Comparator QIV n=227; Overall n=896. For SSP-1 after Dose 1, # of subjects with non-missing data for any local AR and redness: Afluria QIV n=663, Comparator QIV n=226, Overall n=889; and for pain and swelling: Afluria QIV n=663, Comparator QIV n=227, Overall n=890. For SSP-2 after Dose 2, # of subjects with non-missing data for any local AR and redness: Afluria QIV n=349, Comparator n=119, Overall n=468; and for pain and swelling: Afluria QIV n=350; Comparator QIV n=119; Overall n=469.

A total of 896 subjects 6 through 35 months (669 and 227 recipients of Afluria QIV and Comparator QIV, respectively) provided safety data regarding solicited ARs following the first and/or second vaccinations (Solicited Safety Population). Of these subjects, 32.9% and 34.4% of Afluria QIV and Comparator QIV recipients reported any local reaction, primarily pain (20.8% and 25.6%, respectively) and redness (20.8% and 17.6%), followed by swelling (6.1% and 6.2%, respectively). Most reactions were mild to moderate in severity. The rates of any severe local reaction were 0.7% and 2.7% for Afluria QIV and Comparator QIV, respectively. The rates of local reactions were generally similar between treatment groups, with small imbalances in the overall rates of local pain and redness between Afluria QIV and Comparator QIV recipients (as noted). However, the risk of having any severe local reaction was lower for Afluria QIV, relative risk (RR) of 0.28 (95% CI: 0.09, 0.91). The mean onset of all local reactions in the 6 through 35 months age group occurred between Day 1 and Day 2. The mean duration of all local reactions was less than 2 days and was similar between treatment groups.

A total of 890 subjects 6 through 35 months (663 Afluria QIV and 227 Comparator QIV recipients, respectively) provided solicited safety data following the first vaccination (SSP-1) while 469 subjects (350 Afluria QIV and 119 Comparator QIV recipients, respectively) provided solicited safety data following the second vaccination (SSP-2). Pain was the most frequently reported local reaction following both the first and second vaccinations, (overall rates 19.3% and 12.6%, respectively), closely followed by redness (overall 18.1% and 10.2%, respectively). Swelling was much less common following either vaccination (overall 5.4% and 3.0%, respectively). Rates of all three local reactions declined following the second vaccination, were similar between treatment groups, and were mostly mild to moderate in severity.

Solicited Local Adverse Reactions – Subjects 36 through 59 Months

Table 16 summarizes the rates of solicited local ARs reported in the seven days following vaccination (Day 1 through Day 7) in subjects 36-59 months according to dose, treatment, and maximum severity.

Table 16: Solicited Local Adverse Reactions by Dose and Maximum Severity, Subjects 36 through 59 Months (Solicited Safety Population)* – CSLCT-QIV-15-03**

--	Local AR	Afluria N=949	Afluria N=949	Afluria N=949	Afluria N=949	Comp N=318	Comp N=318	Comp N=318	Comp N=318	Overall N=1267
Dose	**Reaction**	**Mild %[1]**	**Mod %[1]**	**Sev %[1]**	**All %[1]**	**Mild %[1]**	**Mod %[1]**	**Sev %[1]**	**All %[1]**	**All %[1]**
Any	Any	35.0	7.0	2.7	44.8	26.2	8.8	5.7	40.9	43.8
Any	Pain	31.7	3.8	0	35.5	27.0	3.8	0.6	31.4	34.5
Any	Swelling	5.8	2.6	1.7	10.1	4.4	5.7	2.5	12.9	10.8
Any	Redness	16.5	3.5	2.3	22.4	10.7	4.7	5.3	20.8	22.0
1st	Any	33.9	6.7	2.6	43.3	25.9	7.6	5.4	38.8	42.2
1st	Pain	30.5	3.4	0	33.9	26.5	2.8	0.3	29.7	32.9
1st	Swelling	5.6	2.6	1.7	9.9	4.1	5.4	2.5	12.0	10.5
1st	Redness	15.8	3.6	2.2	21.8	10.7	4.7	4.7	20.2	21.4

--	Local AR	Afluria N=949	Afluria N=949	Afluria N=949	Afluria N=949	Comp N=318	Comp N=318	Comp N=318	Comp N=318	Overall N=1267
Dose	**Reaction**	**Mild %[1]**	**Mod %[1]**	**Sev %[1]**	**All %[1]**	**Mild %[1]**	**Mod %[1]**	**Sev %[1]**	**All %[1]**	**All %[1]**
2nd	Any	22.9	3.0	0.5	26.4	13.8	6.2	1.5	22.7	25.5
2nd	Pain	19.4	2.0	0	21.4	13.6	4.5	1.5	19.7	21.0
2nd	Swelling	1.0	1.0	0	2.0	1.5	1.5	0	4.5	2.6
2nd	Redness	9.5	0	0.5	10.0	4.5	0	3.0	7.6	9.4

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

*Abbreviations and Populations: AR=adverse reaction; Afluria=Afluria QIV; Comp=Comparator QIV; Mild=Grade 1; Mod=Moderate (Grade 2); Sev=Severe (Grade 3); All=All subjects with a specific local reaction; Any reaction=subjects with any local reaction after any vaccination (based on the Solicited Safety Population after any vaccination, SSP); 1st=subjects with local reaction after first vaccination (based on the Solicited Safety Population after Dose 1, SSP-1); 2nd=subjects with local reaction after second vaccination (based on the Solicited Safety Population after Dose 2, SSP-2).

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[1]Denominators for percentages based on # of subjects with non-missing data for each population, each group, and each parameter. For the SSP, # of subjects with non-missing data for any local AR: Afluria QIV n=947; Comparator QIV n=317; Overall n=1264; for pain: Afluria QIV n=949; Comparator QIV n=318; Overall n=1267; for swelling: Afluria QIV n=949; Comparator QIV n=317; Overall n=1266; for redness: Afluria QIV n=947; Comparator QIV n=318; Overall n=1265. For SSP-1 after Dose 1, # of subjects with non-missing data for any local AR and redness: Afluria QIV n=944, Comparator QIV n=317, Overall n=1261; and for pain and swelling: Afluria QIV n=946, Comparator QIV n=317, Overall n=1263. For SSP-2 after Dose 2, # of subjects with non-missing data for any local AR and swelling: Afluria QIV n=201, Comparator n=65, Overall n=266; and for pain and redness: Afluria QIV n=201; Comparator QIV n=66; Overall n=267.

A total of 1267 subjects 36 through 59 months (949 and 318 recipients of Afluria QIV and Comparator QIV, respectively) provided safety data regarding solicited AEs following the first and/or second vaccinations (Solicited Safety Population). Of these subjects, 44.8% and 40.9% of Afluria QIV and Comparator QIV recipients reported any local reaction, primarily pain (35.5% and 31.4%, respectively), followed by redness (22.4% and 20.8%) and swelling (10.1% and 12.9%), respectively. Most reactions were mild to moderate in severity. The rates of any severe local reaction were 2.7% and 5.7% for Afluria QIV and Comparator QIV, respectively. Although the overall rates of local reactions were similar between treatment groups, the risk of having any severe local reaction was lower Afluria QIV recipients as compared to Comparator QIV, relative risk (RR) of 0.48 (95% CI: 0.27, 0.87). The mean onset of all local reactions in the 36 through 59 months age group occurred between Day 1 and Day 2. The mean duration of all local reactions was less than 2 days and was similar between treatment groups.

A total of 1263 subjects 36 through 59 months (946 Afluria QIV and 317 Comparator QIV recipients, respectively) provided solicited safety data following the first vaccination (SSP-1) while 267 subjects (201 Afluria QIV and 66 Comparator QIV recipients, respectively) provided solicited safety data following the second vaccination (SSP-2). Pain was the most frequently reported local reaction following both the first and second vaccinations, (overall rates 32.9% and 21.0%, respectively), followed by redness (overall 21.4% and 9.4%, respectively). Swelling was much less common following either vaccination (overall 10.5% and 2.6%, respectively). Rates of all three local reactions declined following the second vaccination and were mostly mild to moderate in severity.

In comparison to subjects 6-35 months, subjects 36-59 months in both treatment groups had higher rates of local injection site reactions overall and local reactions assessed as severe.

Cellulitis-like Reaction

Although not solicited as a local adverse reaction in the 7-day electronic diary, subjects were instructed to return to the clinic for evaluation within 24 hours of onset of a cellulitis-like reaction (concurrent Grade 3 injection site pain, erythema, and induration) in the event this occurred within 28 days of any vaccination. One subject reported a cellulitis-like reaction during the study, a 48-month-old recipient of Comparator QIV, on Day 2 following the second vaccination.

Reviewer comment: In 2011 the Applicant reported an increase in postmarketing reports of large injection site swelling and cellulitis and added these events to Section 6.2 (Postmarketing Experience) of the Package Insert. Subsequently, annual Drug Safety Update Reports (DSUR) for Afluria (trivalent formulation, IND 12997), have indicated that these types of postmarketing reports have declined and stabilized. In study CSLCT-QIV-15-03, rates of local injection site reactions in subjects 6 through 59 months were generally similar between treatment groups and did not suggest safety concerns.

Solicited Systemic Adverse Events – Subjects 6 through 35 Months

Table 17 summarizes the rates of solicited systemic AEs reported in the seven days following vaccination (Day 1 through Day 7) in subjects 6-35 months according to dose, treatment, and maximum severity.

Table 17: Solicited Systemic Adverse Events by Dose and Maximum Severity, Subjects 6 through 35 Months (Solicited Safety Population)* – CSLCT-QIV-15-03**

--	--	Afluria N=669	Afluria N=669	Afluria N=669	Afluria N=669	Comp N=227	Comp N=227	Comp N=227	Comp N=227	Overall N=896
Dose	**Systemic AE**	**Mild %[1]**	**Mod %[1]**	**Sev %[1]**	**All %[1]**	**Mild %[1]**	**Mod %[1]**	**Sev %[1]**	**All %[1]**	**All %[1]**
Any	Any	28.3	17.5	3.1	48.9	32.6	13.2	4.0	49.8	49.1
Any	Irritability	19.0	13.2	0.7	32.9	16.7	11.0	0.4	28.2	31.7
Any	Loss of appetite	15.8	3.9	0.3	20.0	16.3	2.6	0.4	19.4	19.9
Any	Nausea and/or vomiting	4.6	4.0	0.7	9.4	9.3	1.8	0	11.0	9.8
Any	Diarrhea	19.4	4.6	0.1	24.2	22.5	2.6	0.4	25.6	24.6
Any	Fever[2]	3.1	1.5	2.5[2]	7.2	6.6	2.6	2.6	11.9	8.4
1st	Any	28.8	14.2	2.3	45.2	31.7	10.1	2.6	44.5	45.1
1st	Irritability	17.5	10.7	0.5	28.7	15.9	7.9	0.4	24.2	27.5
1st	Loss of appetite	12.2	2.6	0.2	14.9	14.1	1.3	0.4	15.9	15.2
1st	Nausea and/or vomiting	3.9	3.0	0.6	7.5	7.9	1.3	0	9.3	8.0
1st	Diarrhea	17.6	3.6	0	21.3	15.9	2.2	0.4	18.5	20.6
1st	Fever[2]	2.3	1.2	1.7[2]	5.1	4.8	1.8	1.3	7.9	5.8
2nd	Any	19.7	10.6	2.0	32.3	20.2	9.2	3.4	32.8	32.4
2nd	Irritability	12.9	6.9	0.9	20.6	10.1	9.2	0	19.3	20.3
2nd	Loss of appetite	10.3	3.1	0.3	13.7	7.6	3.4	0	10.9	13.0
2nd	Nausea and/or vomiting	3.1	2.6	0.3	6.0	4.2	0.8	0	5.0	5.8
2nd	Diarrhea	12.6	2.0	0.3	14.9	18.5	0.8	0	19.3	16.0
2nd	Fever	2.0	0.9	1.7	4.6	4.2	1.7	3.4	9.2	5.8

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.

*Abbreviations and Populations: Afluria=Afluria QIV; Comp=Comparator QIV; Mild=Grade 1; Mod=Moderate (Grade 2); Sev=Severe (Grade 3); All=All subjects with a specific solicited systemic event; Any=subjects with any solicited systemic event after any vaccination (based on the Solicited Safety Population after any

vaccination, SSP); 1st=subjects with solicited systemic event after first vaccination (based on the Solicited Safety Population after Dose 1, SSP-1); 2nd=subjects with solicited systemic event after second vaccination (based on the Solicited Safety Population after Dose 2, SSP-2); AE=adverse event.
**ClinicalTrials.gov identifier: NCT02914275
[1]Denominators for percentages based on # of subjects with non-missing data for each population, each group, and each parameter. For the SSP, # of subjects with non-missing data for any AE, fever, nausea and/or vomiting, diarrhea, loss of appetite, and irritability: Afluria QIV n=669, Comparator QIV n=227, Overall n=896; For the SSP-1, # of subjects with non-missing data for any AE, fever, nausea and/or vomiting, diarrhea, loss of appetite, and irritability: Afluria QIV n=663, Comparator QIV n=227, Overall n=890; For theSSP-2, # of subjects with non-missing data for any AE, fever, nausea and/or vomiting, diarrhea, loss of appetite, and irritability: Afluria QIV n=350, Comparator n=119, Overall n=469.
[2]Subject #(b) (6) (Afluria QIV 6-35 months) erroneously reported having an axillary temperature of 108.5°F on Day 1 following the first vaccination, but actually had no fever. Because the protocol did not allow the Applicant to correct entry errors in patient reported outcomes (electronic diary), the subject is reported in the table as having severe fever after the first vaccination.

Among 896 subjects 6 through 35 months who provided safety data regarding solicited AEs following any (first and/or second) vaccination, 48.9% and 49.8% of Afluria QIV and Comparator QIV recipients, respectively, reported solicited systemic AEs. The most frequently reported symptoms in both groups were irritability (32.9% vs 28.2%), diarrhea (24.4% vs 25.6%), and loss of appetite (20.0% vs 19.4%). Rates were similar between treatment groups with small imbalances observed for irritability (as noted) and fever (Afluria QIV 7.2%, Comparator QIV 11.9%). The relative risk (RR) of fever 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 ≥101.3°F or ≥38.5°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). No fevers were associated with seizures. 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 as noted). The mean onset of solicited systemic AEs was similar between treatment groups, generally between Day 2 and Day 5, with a mean duration of less than two days. 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.

Rates of solicited systemic AEs following the first vaccination were similar to rates following any vaccination, occurring in 45.2% and 44.5% of Afluria QIV and Comparator QIV recipients, respectively. Rates of solicited systemic AEs following the second vaccination were generally lower than the first vaccination in both treatment groups (except for diarrhea and fever in the Comparator QIV group), occurring in 32.3% of Afluria QIV and 32.8% of Comparator QIV recipients. The most common events following the second vaccination with Afluria QIV and Comparator QIV, respectively, were irritability (28.7% vs 24.2%), diarrhea (21.3% vs 18.5%), and loss of appetite (14.9 vs 15.9%). Fever occurred in 5.1% and 7.9% of Afluria QIV and Comparator QIV recipients, respectively, after the first vaccination and in 4.6% and 9.2%, respectively, after the second vaccination. Severe Grade 3 fever (axillary temperature ≥101.3°F or ≥38.5°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. Most events following the first and second vaccination were mild to moderate in severity. A total of 2.3% and 2.6% of Afluria QIV and Comparator QIV recipients, respectively, reported severe solicited systemic AEs following the first vaccination, and 2.0% and 3.4%, respectively, after the second vaccination.

Reviewer comment: Although there were small imbalances in rates of various solicited system AEs between treatment groups, e.g., slightly higher rates of irritability among recipients of Afluria QIV, and slightly higher rates of fever and nausea and/or vomiting in recipients of Comparator QIV, no large imbalances or unusual patterns were observed. The rate of fever after any vaccination was slightly lower among Afluria QIV recipients (7.2%) as compared to Comparator QIV (11.9%), and was lower than historical rates in this age group [please see Section 2.4].

Reviewer comment: Rates of severe fever in children 6-35 months after any vaccination were similar between treatment groups (Afluria QIV 2.5%, Comparator QIV 2.6%). The mother of Subject #(b) (6) (Afluria QIV 6-35 months) erroneously reported having an axillary temperature of 108.5°F on Day 1 following the first vaccination, but the child had no fever (see case narrative under Severe Grade 3 Solicited Fever). Because the protocol did not allow the Applicant to correct entry errors in patient reported outcomes (i.e., the electronic diary), the subject was reported in the CSR as having severe fever after the first vaccination. If Subject #(b) (6) was excluded from the analysis, the differences in reported (7.2% and 2.5%) and actual rates (7.0% and 2.4%) of solicited fever and severe fever, respectively, among Afluria QIV recipients 6 – 35 months are not clinically significantly different. Therefore, we will use the Applicant's more conservative subject reported rates throughout this review and in the PI for consistency of numerical presentation.

Solicited Systemic Adverse Events – Subjects 36 through 59 Months

Table 18 summarizes the rates of solicited systemic AEs reported in the seven days following vaccination (Day 1 through Day 7) in subjects 36-59 months according to treatment and maximum severity.

Table 18: Solicited Systemic Adverse Events by Maximum Severity, Subjects 36 through 59 Months (Solicited Safety Population) – CSLCT-QIV-15-03*

--	--	Afluria N=949	Afluria N=949	Afluria N=949	Afluria N=949	Comp N=318	Comp N=318	Comp N=318	Comp N=318	Overall N=1267
Dose	**Systemic AE**	**Mild %[1]**	**Mod %[1]**	**Sev %[1]**	**All %[1]**	**Mild %[1]**	**Mod %[1]**	**Sev %[1]**	**All %[1]**	**All %[1]**
Any	Any	21.8	8.4	2.0	32.2	24.8	5.7	1.6	32.1	32.2
Any	Headache	4.4	1.4	0.4	6.2	4.7	0.3	0	5.0	5.9
Any	Myalgia	7.9	1.9	0.1	9.9	8.2	1.3	0	9.4	9.8
Any	Malaise and Fatigue	8.3	5.5	0.5	14.3	8.5	4.4	0.3	13.2	14.0
Any	Nausea and/or Vomiting	5.3	3.5	0.4	9.2	4.1	2.2	0.3	6.6	8.5
Any	Diarrhea	10.3	1.7	0.1	12.1	7.5	0.6	0.6	8.8	11.3
Any	Fever	2.6	1.1	1.2	4.8	3.8	1.3	0.9	6.0	5.1
1st	Any	21.1	7.6	1.9	30.7	22.7	4.1	1.3	28.1	30.0
1st	Headache	4.2	1.3	0.3	5.8	3.8	0.3	0	4.1	5.4
1st	Myalgia	7.4	1.9	0.1	9.4	6.9	0.6	0	7.6	8.9
1st	Malaise and Fatigue	7.8	4.7	0.5	13.0	7.9	3.8	0	11.7	12.7
1st	Nausea and/or Vomiting	5.1	3.2	0.3	8.6	3.5	1.6	0	5.0	7.7
1st	Diarrhea	9.5	1.5	0.1	11.1	6.3	0.6	0.3	7.3	10.1
1st	Fever	2.1	1.0	1.2	4.2	3.8	0.9	0.9	5.7	4.6
2nd	Any	8.0	5.5	1.0	14.4	13.6	10.6	1.5	25.8	17.2

--	--	Afluria N=949	Afluria N=949	Afluria N=949	Afluria N=949	Comp N=318	Comp N=318	Comp N=318	Comp N=318	Overall N=1267
Dose	**Systemic AE**	**Mild %[1]**	**Mod %[1]**	**Sev %[1]**	**All %[1]**	**Mild %[1]**	**Mod %[1]**	**Sev %[1]**	**All %[1]**	**All %[1]**
2nd	Headache	1.0	1.0	0.5	2.5	4.5	0	0	4.5	3.0
2nd	Myalgia	3.0	0	0.5	3.5	6.1	3.0	0	9.1	4.9
2nd	Malaise and Fatigue	4.0	5.0	0	9.0	6.1	3.0	1.5	10.6	9.4
2nd	Nausea and/or Vomiting	2.0	1.5	0.5	4.0	3.0	3.0	1.5	7.6	4.9
2nd	Diarrhea	5.5	2.0	0	7.5	7.6	0	1.5	9.1	7.9
2nd	Fever	2.5	0.5	0.5	3.5	1.5	1.5	0	3.0	3.4

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.

*Abbreviations and Populations: Afluria=Afluria QIV; Comp=Comparator QIV; Mild=Grade 1; Mod=Moderate (Grade 2); Sev=Severe (Grade 3); All=All subjects with a specific solicited systemic event; Any=subjects with any solicited systemic event after any vaccination (based on the Solicited Safety Population after any vaccination, SSP); 1st=subjects with solicited systemic event after first vaccination (based on the Solicited Safety Population after Dose 1, SSP-1); 2nd=subjects with solicited systemic event after second vaccination (based on the Solicited Safety Population after Dose 2, SSP-2); AE=adverse event.

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[1]Denominators for percentages based on # of subjects with non-missing data for each population, each group, and each parameter. For the SSP, # of subjects with non-missing data for any AE, fever, nausea and/or vomiting, diarrhea, headache, myalgia, and malaise and fatigue: Afluria QIV n=949, Comparator QIV n=318, Overall n=1267; For the SSP-1, # of subjects with non-missing data for any AE, fever, nausea and/or vomiting, diarrhea, headache, myalgia and malaise and fatigue: Afluria QIV n=946, Comparator QIV n=317, Overall n=1263; For the SSP-2, # of subjects with non-missing data for any AE, fever, nausea and/or vomiting, diarrhea, headache, myalgia, and malaise and fatigue: Afluria QIV n=201, Comparator n=66, Overall n=267.

Among 1267 subjects 36 through 59 months who provided safety data regarding solicited AEs following any (first and/or second) vaccination, 32.2% and 32.1% of Afluria QIV and Comparator QIV recipients, respectively, reported solicited systemic AEs. The most frequently reported symptoms in both groups were malaise and fatigue (14.3% vs 13.2%), myalgia (9.9% vs 9.4%), and diarrhea (12.1% vs 8.8%). Rates were similar between treatment groups with small imbalances observed for diarrhea (as noted), nausea and/or vomiting (Afluria QIV 9.2%, Comparator QIV 6.6%), and fever (Afluria QIV 4.8%, Comparator QIV 6.0%). 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 ≥101.3°F or ≥38.5°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). No fevers were associated with seizures. 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 as noted). Most solicited systemic AEs had onset between Day 2 and Day 4 after vaccination, with a mean duration of less than two days. 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.

Rates of solicited systemic AEs following the first vaccination were similar to but slightly lower than rates following any vaccination, occurring in 30.7% and 28.1% of Afluria QIV and Comparator QIV recipients, respectively. Rates of solicited systemic AEs following the second vaccination were lower than the first vaccination in the Afluria QIV group

(overall 14.4%) but were only slightly lower in the Comparator QIV group (overall 25.8%). The most common events following the second vaccination with Afluria QIV and Comparator QIV, respectively, were malaise and fatigue (9.0% vs 10.6%) and diarrhea (7.5% vs 9.1%). As compared to Afluria QIV, Comparator QIV recipients also had more myalgia (9.1% vs 3.5%) and nausea and/or vomiting (7.6% vs 4.0%) following the second vaccination. Fever occurred in 4.2% and 5.7% of Afluria QIV and Comparator QIV recipients, respectively, after the first vaccination and in 3.5% and 3.0%, respectively, after the second vaccination. Severe Grade 3 fever (axillary temperature ≥101.3°F or ≥38.5°C) occurred in 1.2% and 0.9% of Afluria QIV and Comparator QIV recipients, respectively, after the first vaccination, and in 0.5% and none, respectively, after the second vaccination. Most events following the first and second vaccination were mild to moderate in severity. A total of 1.9% and 1.3% of Afluria QIV and Comparator QIV recipients, respectively, reported severe solicited systemic AEs following the first vaccination, and 1.0% and 1.5%, respectively, after the second vaccination.

Reviewer comment: Rates of solicited systemic AEs in children 36-59 months were similar between treatment groups overall and after the first vaccination. Recipients of Afluria QIV had less systemic reactogenicity after the second vaccination and less fever overall as compared to recipients of Comparator QIV although the RR was not statistically significant [Afluria QIV 4.8%, Comparator QIV 6.0% (RR = 0.81, 95% CI: 0.48, 1.36)].

Severe (Grade 3) Solicited Fever

The electronic datasets were evaluated further and case narratives requested for the 23 subjects [Afluria QIV = 17 (2.5%), Comparator QIV = 6 (2.6%)] in the 6-36 months age stratum and 14 subjects [Afluria QIV = 11 (1.2%), Comparator QIV = 3 (0.9%)] in the 36-59 months age stratum who experienced severe (Grade 3) fever, defined as axillary temperature ≥101.3°F (≥38.5°C), following any vaccination. All Grade 3 solicited fever AEs were non-serious. Nine of 28 (32.1%) Afluria QIV recipients and 3 of 9 (33.3%) of Comparator QIV recipients had onset of severe fever within 48 hours of vaccination. Most severe febrile episodes were treated with acetaminophen and/or ibuprofen and resolved within 1-2 days. Seventeen of 28 (60.7%) Afluria QIV recipients and 5 of 9 (55.6%) Comparator QIV recipients had severe fever assessed as related to study vaccine.

Two Afluria QIV recipients who experienced severe (Grade 3) fever were notable, and case report forms (CRFs) were requested for review:

- Subject #(b) (6) was a 40-month-old black/African American female without relevant medical history, who last received influenza vaccine in 2014. She experienced fever of 103.6°F on Day 4 following the first dose of Afluria QIV. Beginning on Day 3 post-vaccination, she also had solicited moderate headache, severe myalgia, severe malaise and fatigue, and unsolicited ILI. Her parents sought medical advice, and she was treated with acetaminophen and defervesced by Day 5. She was evaluated for ILI at the study site and had a negative PCR for influenza A and B. The fever and associated symptoms were assessed as related to vaccination. Review of the CRF indicated that, because she had no protocol-defined contraindications to the second vaccination, e.g., fever of >103.1°F within 48 hours of the first vaccination or seizure, the subject received Dose 2. On Day 4 following the second vaccination, she again experienced Grade 3 fever (102.5°F) assessed as related to vaccination, and

defervesced that same day (no antipyretic reported). Associated solicited symptoms began on the day of the second vaccination and included severe nausea and/or vomiting, moderate headache, severe myalgia, and moderate malaise and fatigue. An unsolicited AE of ILI was reported on Day 4 to Day 6 post-Dose 2, evaluated with a PCR, and was negative for influenza.

- Subject #(b) (6) was a 10-month-old black/African American female without relevant medical history who had no prior history of influenza vaccination. She was afebrile prior to the first vaccination (Day 1, (b) (6)) and had no immediate reactions during the 30-minute post-vaccination observation period. Her mother made an erroneous entry of axillary temperature of 108.5°F in the solicited AE diary on the evening of Day 1 and called to notify the study site of the error. In fact, no temperature had been taken. At the investigator's request, the mother returned to the study site the next morning where the child was noted to be afebrile and playful without a change in health status. Although the parent reported her child to have had irritability (recorded as moderate and not related to vaccination) on Days 2 and 3, she confirmed that the child had no fever at any time after the first vaccination. The subject received the second study vaccination but her parents/guardian did not record solicited symptoms in the diary following the second dose.

Reviewer comment: Evaluation of the electronic datasets confirmed the Applicant's initial case narrative for Subject #(b) (6) and yielded no other relevant information. The CRF (page 191-193) indicated a fever of 108.5°F on (b) (6) , and an "Entry Error" for causality. In response to a request for additional information, the Applicant provided the above clarification, a copy of the audit trail not provided in the CRF, and also clarified that the temperature entry was not corrected in the electronic diary or the Electronic Data Capture (EDC) system because modifications of patient reported outcomes were not allowed. Therefore, the subject was counted as having had a severe (Grade 3) fever on Day 1 in the Solicited AE data tables and PI. To reconcile the discrepancy without changing the patient reported outcome or Applicant's report, the reviewer has added explanatory footnotes to relevant tables in this review.

Reviewer comment: Severe (Grade 3) fever was notable in two recipients of Afluria QIV: in one because fever and moderate to severe solicited systemic reactogenicity symptoms followed both vaccinations, and in the other because of an erroneous entry of very high fever following the first vaccination (108.5°F). The overall rates of severe (Grade 3) fever in the 7 days following any vaccination were generally low and similar between treatment groups. Additionally, in the reviewer's opinion, relatedness of severe fever to study vaccine was uncertain in some cases due to concurrent upper respiratory or gastrointestinal symptoms possibly suggestive of intercurrent viral infections.

Reviewer comment: The rate of fever in the 7 days following any vaccination was statistically significantly lower in recipients of Afluria QIV (5.8%) as compared to Comparator QIV (8.4%) in the overall population of subjects 6 through 59 months, RR: 0.69 (95% CI: 0.49, 0.97). Rates were lower than in previous pediatric trials of Afluria (trivalent), and appear comparable to rates of fever in pediatric populations following vaccination with other inactivated influenza vaccines (based on data in other PIs). No episodes of solicited fever were associated with seizures. Although exposure to Afluria QIV in this trial was relatively small, the data support

the Applicant's hypothesis that (b) (4) ***can reduce the pyrogenicity of the vaccine in the pediatric population 6-59 months. We note, however, that the study was not adequately powered to detect all clinically significant difference in the rates of febrile seizures between treatment groups. Greater postmarketing exposure and surveillance will help determine whether the lower rates of fever observed in CSLCT-QIV-15-03 are generalizable to a broader population of children 6-59 months or to future vaccine formulations containing different antigens. The occurrence of febrile adverse reactions and febrile seizures will be monitored closely by OBE/DE through postmarketing surveillance.***

Reviewer comment: Overall, rates of solicited systemic AEs in both age strata (6-59 months), including fever and severe AEs, in recipients of Afluria QIV were acceptable without unusual patterns or safety concerns. The number and rates of each solicited local and systemic AE by maximum severity as determined by evaluation of the electronic datasets were identical to the Applicant's report.

Subpopulation Analyses of Solicited Adverse Events

Sex

Among the pediatric population 6-59 months, 38.4% and 41.5% of male and female recipients of Afluria QIV, respectively, experienced solicited local injection site reactions. Differences in rates of local reactions between males and females, respectively, were as follows: pain 28.7% vs 30.2%; swelling 8.3% vs 8.6%; and redness 20.3% vs 23.4%. Among the pediatric population 6-59 months, 39.1% and 39.2% of male and female recipients of Afluria QIV experienced solicited systemic AEs. Differences in rates of specific events between male and female subjects 6-59 months, respectively, were as follows: fever 6.3% vs 5.3%; nausea and/or vomiting 10.1% vs 8.3%; and diarrhea 18.2% vs 15.9%. Differences in rates of events in male and female subjects, respectively, specific to the 6-35 months age group were: loss of appetite 21.7% vs 18.2% and irritability 32.5% vs 33.3%. Differences in rates of events in male and female subjects, respectively, specific to the 36-59 months age group were: headache 6.1% vs 6.4%; myalgia 10.7% vs 9.0%; and malaise/fatigue 14.0% vs 14.7%.

Reviewer comment: Subpopulation analyses showed similar rates of solicited local and systemic adverse events between male and female recipients of Afluria QIV.

Race

Among the pediatric population 6-59 months, 30.0% and 43.0% of black/African American and white recipients of Afluria QIV, respectively, experienced solicited local injection site reactions. Differences in rates of local reactions between blacks/African Americans and whites, respectively, were as follows: pain 26.0% vs 30.4%; swelling 5.2% vs 9.4%; and redness 11.0% vs 25.4%. Among the pediatric population 6-59 months, 28.1% and 42.8% of black/African American and white recipients of Afluria QIV, respectively, experienced solicited systemic AEs. Differences in rates of events between black/African American and white subjects 6-59 months, respectively, were as follows: fever 5.5% vs 6.0%; nausea and/or vomiting 9.2% vs 9.1%; and diarrhea 15.0% vs 18.5%. Differences in rates of events between black/African American and white subjects, respectively, specific to the 6-35 months age group were: loss of appetite 14.0% vs 21.4% and irritability 18.6% vs 36.1%. Differences in rates of events between black/African American and white subjects, respectively, specific to the 36-59 months

age group were: headache 6.6% vs 6.5%; myalgia 5.6% vs 11.8%; and malaise/fatigue 12.1% vs 15.0%.

Reviewer comment: Black/African American recipients of Afluria QIV showed a trend towards lower rates of solicited local injection site and systemic adverse events as compared to whites, with the largest imbalances observed in the rates of any solicited local AR (30.0% vs 43.0%), injection site redness (11.0% vs 25.4%), any systemic AE (28.1% vs 42.8%), and irritability (18.6% vs 36.1%). Small sample sizes precluded meaningful analyses of racial subgroups other than blacks/African Americans and whites.

Ethnicity
Among the pediatric population 6-59 months, 36.1% and 41.2% of Hispanic/Latino and non-Hispanic/Latino recipients of Afluria QIV, respectively, experienced solicited local injection site reactions. Differences in rates of local reactions between Hispanic/Latino and non-Hispanic/Latino, respectively, were as follows: pain 25.3% vs 30.8%; swelling 7.0% vs 9.0%; and redness 18.1% vs 23.1%. Among the pediatric population 6-59 months, 32.3% and 41.4% of Hispanic/Latino and non-Hispanic/Latino recipients of Afluria QIV experienced solicited systemic AEs. Differences in rates of events between Hispanic/Latino and non-Hispanic/Latino subjects 6-59 months, respectively, were as follows: fever 6.5% vs 5.5%; nausea and/or vomiting 9.4% vs 9.1%; and diarrhea 10.4% vs 19.5%. Differences in rates of events between Hispanic/Latino and non-Hispanic/Latino subjects, respectively, specific to the 6-35 months age group were: loss of appetite 18.6% vs 20.6% and irritability 26.8% vs 35.3%. Differences in rates of events between Hispanic/Latino and non-Hispanic/Latino subjects, respectively, specific to the 36-59 months age group were: headache 4.3% vs 6.9%; myalgia 7.8% vs 10.7%; and malaise/fatigue 10.8% vs 15.4%.

Reviewer comment: Overall, Hispanic/Latino recipients of Afluria QIV 6-59 months showed a trend towards lower rates of solicited local and systemic adverse events as compared to non-Hispanic/Latinos.

Reviewer comment: Overall, subpopulation analyses showed no large differences in solicited AEs by sex and trends towards lower rates of solicited local and systemic AEs in blacks/African Americans and Hispanic/Latinos as compared to whites and non-Hispanic/Latinos. However, the data do not allow firm conclusions because CSLCT-QIV-15-03 was not designed to demonstrate statistically significant differences in rates of solicited local and systemic AEs between subpopulations using inferential statistics. The descriptive comparisons represent trends that may have been due to chance. Small sample sizes precluded meaningful analyses of racial subgroups other than blacks/African Americans and whites.

Exploratory Endpoint of Antipyretic Use
The frequency of antipyretic use in the seven days following each study vaccination in the Per Protocol population was a pre-specified exploratory endpoint. Because the Safety Population was the most clinically relevant population, the Applicant was asked to repeat the analyses using the Safety and Solicited Safety Populations (post hoc exploratory analyses). Table 19 presents the frequency of antipyretic use in the seven days following each vaccination according to treatment, age group, and overall. Antipyretic medications were identified by the WHO drug dictionary (version March

2016) ATC code N02B, and included acetaminophen and ibuprofen. A majority (56.6%) of subjects reported using antipyretics for one day, 17.0% for two days, 9.4% for three days, and the remainder (19.5%) for 4 to 10 days (data not shown).

Table 19: Antipyretic use in the 7 Days after Vaccination by Treatment and Age Group (Safety Population) – CSLCT-QIV-15-03*

Subjects 6-59 months	**Antipyretic Use / Vaccination**	**Afluria QIV N=1673**	**Comparator QIV N=559**	**Overall N=2232**
--	First n(%)	65 (3.9)	22 (3.9)	87 (3.9)
--	Second n(%)	15 (0.9)	8 (1.4)	23 (1.0)
--	Any n(%)	77 (4.6)	29 (5.2)	106 (4.7)
Subjects 6-35 months	**Antipyretic Use / Vaccination**	**Afluria QIV N=694**	**Comparator QIV N=233**	**Overall N=927**
--	First n(%)	33 (4.8)	15 (6.4)	48 (5.2)
--	Second n(%)	11 (1.6)	6 (2.6)	17 (1.8)
--	Any n(%)	41 (5.9)	21 (9.0)	62 (6.7)
Subjects 36-59 months	**Antipyretic Use / Vaccination**	**Afluria QIV N=979**	**Comparator QIV N=326**	**Overall N=1305**
--	First n(%)	32 (3.3)	7 (2.1)	39 (3.0)
--	Second n(%)	4 (0.4)	2 (0.6)	6 (0.5)
--	Any n(%)	36 (3.7)	8 (2.5)	44 (3.4)

Source: STN 125254/692/5, Module 5, CSLCT-QIV-15-03 CSR, Additional Analyses, Final Tables 14.2.7.1.1, 14.2.7.1.2, 14.7.2.1.3, 14.2.7.2.1, 14.2.7.2.2, and 14.2.7.2.3.
*ClinicalTrials.gov identifier: NCT02914275.

Reviewer comment: Antipyretic use in the seven days after any vaccination in children 6-59 months was relatively low, 4.7% of the overall Safety Population, and generally similar between treatment groups, overall (Afluria QIV 4.6%; Comparator QIV 5.2%) and within age strata. A trend towards higher frequency of use was observed in the younger as compared to the older age stratum (6.7% vs 3.4%) and, for both age strata, after the first as compared to the second vaccinations (3.9% vs 1.0%). The pattern of antipyretic use reflected the occurrence of fever in the study population (Section 6.1.12.2).

Unsolicited Adverse Events (Day 1 through Day 28)

Only treatment emergent AEs (TEAE), i.e., those that began or were exacerbated after exposure to study treatment, were included in the analyses of unsolicited AEs. Multiple occurrences of the same AE were counted only once per subject. AEs were coded according to MedDRA Preferred Term (PT) and System Organ Class (SOC), version 19.0.

Please see Table 14 [at beginning of Sect 6.1.12.2] for an overview of unsolicited AEs, and CSLCT-QIV-15-03 CSR (STN 125254/692) Tables 12.2.2-5, 12.2.2-6, 14.3.1.7.1.2, 14.3.1.7.2.2, 14.3.1.8.1.2, 14.3.1.8.2.2, 14.3.1.9.1.2, 14.3.1.9.2.2, 14.3.1.9.3.1, and 14.3.1.9.3.2 for detailed summaries of unsolicited AEs by PTs and SOCs reported in each treatment group according to age groups 6-59 months, 6-35 months, and 36-59 months.

A total of 707 subjects (31.7%) 6 through 59 months reported 1,547 spontaneous or unsolicited AEs in the 28 days following vaccination, with similar frequencies between treatment groups (Afluria QIV 32.0%, Comparator QIV 30.6%). 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. Small imbalances in rates of individual events as categorized

by PT were observed between treatment groups, however, rates as categorized by SOC were similar. Among subjects 6-35 months who received Afluria QIV, the most common unsolicited AEs (frequency ≥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%). The most common AEs (frequency ≥1%) among Comparator QIV recipients were: rhinorrhea (13.7%), cough (9.9%), otitis media (4.7%), pyrexia (4.7%), upper respiratory tract infection (3.0%), irritability (3.0%), diarrhea (3.0%), vomiting (3.0%), fatigue (2.6%), nasopharyngitis (2.1%), teething (1.7%), decreased appetite (1.3%), sneezing (1.3%), rash (1.3%), and influenza-like illness (1.3%). In both treatment groups, most AEs were assessed as mild (61.8% of all events occurring in 19.4% of all subjects 6-35 months) or moderate (32.0% of all events occurring in 14.7% of all subjects 6-35 months) in severity, while 3.7% and 3.0% of Afluria QIV and Comparator QIV recipients, respectively, experienced severe AEs (7.0% and 3.9% of all AEs in the respective groups were severe). Fewer Afluria QIV recipients than Comparator QIV (9.5% vs 10.7%, respectively) had unsolicited AEs assessed as related to study vaccine by the investigator.

Reviewer comment: Analyses of unsolicited AEs in children 6-35 months showed small imbalances trending towards more upper respiratory tract infection, ear infection, croup infectious, and pyrexia in Afluria QIV recipients and more otitis media, pharyngitis streptococcal, decreased appetite, irritability, and fatigue in Comparator QIV recipients. Overall, rates of unsolicited AEs were low and generally similar between treatment groups with no large clinically significant imbalances or unusual patterns.

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. No large imbalances were observed. The most common unsolicited AEs (frequency ≥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%). The most common unsolicited AEs (frequency ≥1%) among recipients of Comparator QIV were rhinorrhea (6.1%), cough (5.2%), pyrexia (2.8%), upper respiratory tract infection (2.5%), vomiting (1.8%), and nasal congestion (1.5%). Most subjects in both treatment groups had AEs assessed as mild (60.6% of all events occurring in 55.0% of all subjects 36-59 months) or moderate (33.4% of all events occurring in 37.7% of all subjects months) in severity, while 1.9% and 2.1% of Afluria QIV and Comparator QIV recipients, respectively, experienced severe AEs (6.1% and 5.3% of all AEs in the respective groups were severe). As in the younger age cohort, fewer Afluria QIV recipients than Comparator QIV (7.8% vs 8.3%, respectively) had unsolicited AEs assessed as related to study vaccine by the investigator.

Reviewer comment: More unsolicited AEs were reported by subjects 6-35 months as compared to 36-59 months, overall, 37.6% vs 27.4%, respectively. Overall rates of unsolicited AEs between treatment groups were similar within each age stratum (37.6% vs 37.8% and 28.1% vs 25.5%, respectively). No large imbalances or unusual patterns of specific events were observed. No subjects had missing data regarding the severity of an unsolicited AE. Evaluation of the electronic datasets yielded numbers of AEs identical to the Applicant's report.

Reviewer comment: The severity and relatedness of unsolicited AEs were reviewed in detail. Evaluation of the electronic datasets yielded results for severe unsolicited AE consistent with the CSR text, tables (14.3.1.9.1.2, 14.3.1.9.4.2, 14.3.1.8.1.2, and 14.3.1.8.2.2) and listings (16.2.7.2). Severe (Grade 3) unsolicited AEs were varied in type without unusual patterns or imbalances between treatment groups. Overall, severe pyrexia was reported in 14 (0.8%) Afluria QIV and 5 (0.9%) Comparator QIV recipients. One subject in each group experienced non-serious severe pyrexia assessed as related to the study vaccine. Afluria QIV subject #(b) (6) , an 8-month-old female, experienced a fever of 102.0°F beginning ten days after receiving the second vaccination, lasting a total of 5 days. Medical advice was sought and the fever resolved without specific medical therapy. Evaluation of the datasets revealed that this subject also had an AE of "ear infection" that began on the same day as her fever and lasted 11 days, resolving after treatment with amoxicillin. In this reviewer's opinion, the late onset of fever, prolonged duration, and concomitant ear infection suggest that fever in this subject was more likely related to an otitis media than Afluria QIV. Comparator QIV subject #(b) (6) , a 16-month-old female, experienced fever (not measured) beginning 8 days after the first vaccination, lasting 5 days. Vomiting accompanied the fever for approximately the same duration. Medical advice was sought, no specific medications administered, and the fever resolved. Relatedness of fever and vomiting to study vaccine in this subject is also uncertain in the opinion of this reviewer.

Seizures

The CSR tables and electronic datasets were evaluated for all cases of seizures and convulsions, with or without fever. Two subjects experienced febrile seizures (described further in Section 6.1.12.4), #(b) (6) , both female recipients of single dose Afluria QIV in the 6-35 months age group. Febrile seizures occurred 43 and 104 days, respectively, post-vaccination, and were assessed as not related to study vaccine. Subject #(b) (6) had a seizure assessed as severe (Grade 3), one day in duration, and recovered. Subject #(b) (6) had a seizure assessed as mild (Grade 1) in severity, one day in duration, and recovered.

Reviewer comment: The two febrile seizures (0.1% of Afluria QIV recipients) were not related to study vaccine. The background rate of febrile seizures is 2%-5% of children between 6 to 60 months, with a 3-fold higher risk in children 6-16 months. The study was not adequately powered to detect all clinically significant differences in the rates of febrile seizures between treatment groups or relative to background rates using inferential statistics. [1]

Hypersensitivity-Type Adverse Events

The CSR and electronic datasets were evaluated for Unsolicited AEs (MedDRA preferred and verbatim terms) suggestive of hypersensitivity reactions in the 28 days following vaccinations [e.g., dyspnoea, hypersensitivity, pruritus, lip swelling, swelling face, various terms for rash, urticaria, wheezing, stridor, injection site excoriation/erosion]. Almost all AEs were mild/Grade 1 in severity. None were Grade 3 or serious. Most were assessed as not related to study vaccine (e.g., AEs of dyspnoea, wheezing, and stridor were associated with upper respiratory infections). Events occurred in both treatment groups in low frequencies, ranging 0.06% to 0.9%, without large imbalances.

Reviewer comment: Unsolicited AEs potentially representing hypersensitivity reported in the 28 days following vaccinations were not serious, were mostly mild, and appeared unrelated to study vaccines and/or clinically insignificant. This reviewer questioned the accuracy of some of the investigator assessments of relatedness. For example, Subject #(b) (6) , a 21-month-old female, received Seqirus QIV on Day 1 and had onset of moderate/Grade 2 stridor on Day 5, associated with bilateral conjunctivitis, rhinorrhea and croup, all assessed as related to study vaccine rather than to a viral infection (e.g. parainfluenza). Overall, rates were low and balanced between treatment groups. Hypersensitivity reactions following influenza vaccines are not unexpected. Serious immediate hypersensitivity reactions following influenza vaccination are rare and did not occur in this study.

Subpopulation Analyses of Unsolicited Adverse Events (through Day 28)
Overall, males in both treatment groups (Afluria QIV 34.3%, Comparator QIV 35.9%) experienced more unsolicited AEs in the 28 days following vaccination than females (Afluria QIV 29.7%, Comparator QIV 24.6%), but differences in specific events were small. Among Afluria QIV recipients, differences between males and females in the rates of specific events as categorized by SOC were <3%, and as categorized by PT <2%. For additional information, please refer to CSLCT-QIV-15-03 CSR Table 14.3.1.7.3.2.

Sub-analyses of racial groups revealed lower rates of unsolicited AEs in blacks/African Americans, who comprised 21.3% of the Overall Safety Population (OSP), as compared to whites (71.7% of the OSP). Overall rates of unsolicited AEs in black/African Americans vs white Afluria QIV recipients were 19.0% and 35.9%, respectively, and, among Comparator QIV recipients, 23.1% and 33.2%, respectively. Among Afluria QIV recipients, the largest disparities in rates of unsolicited AEs between blacks/African Americans and whites, respectively, were observed in the SOC categories of Infections and Infestations (5.3% vs 14.1%), Respiratory, Thoracic and Mediastinal Disorders (8.7% vs 16.8%), Gastrointestinal Disorders (3.1% vs 6.9%), and General Disorders and Administration Site Conditions (2.8% vs 9.4%). The largest disparities in rates of AEs between blacks/African Americans and whites, respectively, as categorized by PT were: pyrexia, excluding temperature recorded in solicited AE diary through Day 7, (1.7% vs 5.9%), cough (5.0% vs 10.2%), rhinorrhea (4.8% vs 8.6%), and upper respiratory tract infection (1.4% vs 3.9%). The reason for the trend towards higher rates of reported unsolicited pyrexia and respiratory symptoms in white recipients of Afluria QIV is unknown. Small sample sizes precluded meaningful sub-analyses of unsolicited AEs in other racial groups. For additional information, please refer to CSLCT-QIV-15-03 CSR Table 14.3.1.7.4.2.

Hispanic/Latinos comprised 25.7% of the OSP. In both treatment groups, the overall rates of unsolicited AEs were lower in Hispanic/Latinos as compared to non-Hispanic/Latinos (Afluria QIV 28.4% vs 33.4%; Comparator QIV 22.8% vs 33.9%). The greatest differences between Hispanic/Latinos and non-Hispanic/Latinos, respectively, among Afluria QIV recipients occurred in the SOC of Respiratory, Thoracic, and Mediastinal Disorders (11.6% vs 16.0%). The largest disparities in the rates of individual AEs as categorized by PT between Hispanic and non-Hispanic recipients of Afluria QIV were upper respiratory tract infection (5.8% vs 2.6%) and cough (5.1% vs 10.%) For additional information, please refer to CSLCT-QIV-15-03 CSR Table 14.3.1.7.5.2.

Reviewer comment: Subpopulation analyses in Afluria QIV recipients showed trends towards higher rates of unsolicited AEs in males, whites, and non-Hispanic/Latinos as compared to females, blacks/African Americans, Hispanic/Latinos, respectively. However the comparisons are limited by small sample sizes and the descriptive nature of the analyses, and we cannot draw firm conclusions from the observed trends.

6.1.12.3 Deaths

No deaths were reported during the study.

6.1.12.4 Nonfatal Serious Adverse Events

A total of 14 subjects, 11 (0.7%) Afluria QIV and 3 (0.5%) Comparator QIV recipients, reported 15 SAEs from Day 1 through the final database lock (approximately 180 days post-vaccinations). All SAEs occurred in the 6-35 months age stratum except for one SAE experienced by a Comparator QIV recipient in the 36-59 months age stratum. Eleven of 15 SAEs occurred more than 28 days after the most recent vaccination. Table 20 summarizes all SAEs that occurred from Day 1 through ~180 days post-vaccination(s) in each subject, by MedDRA SOC, PT, and treatment group.

Table 20: Frequency of Serious Adverse Events, from Day 1 through Day 180, According to MedDRA System Organ Class, Preferred Term, and Treatment Group – Subjects 6 through 59 Months (Overall Safety Population) – CSLCT-QIV-15-03*

System Organ Class (SOC) • Preferred Term (PT)	**Afluria QIV N=1673 n(%)**	**Comparator QIV N=559 n(%)**	**Overall N=2232 n(%)**
≥1 SAE – 6-59 months	11 (0.7)	3 (0.5)	14 (0.6)
≥1 SAE – 6-35 months**	11 (1.6)	2 (0.9)	13 (1.4)
≥1 SAE – 36-59 months**	0	1 (0.3)	1 (0.1)
Infections and infestations	5 (0.3)	1 (0.2)	6 (0.3)
• Croup infectious***	2 (0.1)	0	2 (0.1)
• Bronchiolitis	0	1 (0.2)	1 (<0.1)
• Pneumonia respiratory syncytial viral	1 (0.1)	0	1 (<0.1)
• Respiratory syncytial virus bronchiolitis	1 (0.1)	0	1 (<0.1)
• Respiratory syncytial virus infection	1 (0.1)	0	1 (<0.1)
Metabolic and nutrition disorders	1 (0.1)	0	1 (<0.1)
• Dehydration***	1 (0.1)	0	1 (<0.1)
Nervous system disorders	2 (0.1)	0	2 (0.1)
• Febrile convulsion	2 (0.1)	0	2 (0.1)
Respiratory, thoracic and mediastinal disorders	1 (0.1)	0	1 (<0.1)
• Pneumonitis	1 (0.1)	0	1 (<0.1)
Gastrointestinal disorders	1 (0.1)	1 (0.2)	2 (0.1)
• Dysphagia	1 (0.1)	0	1 (<0.1)
• Impaired gastric emptying	0	1 (0.2)	1 (<0.1)
Injury, poisoning, and procedural complications	2 (0.1)	1 (0.2)	3 (0.1)
• Animal bite	1 (0.1)	0	1 (<0.1)
• Foreign body aspiration	1 (0.1)	0	1 (<0.1)
• Humerus fracture	0	1 (0.2)	1 (<0.1)

Source: Adapted from STN 125254/692, Module 5, CSLCT-QIV-15-03 CSR, Tables 12.3-2, 14.3.1.10.1.1, 14.3.1.10.1.2, and 14.3.1.10.1.3, and the electronic datasets.
*ClinicalTrials.gov identifier: NCT02914275.
**Percentages based on number of subjects in the respective treatment groups of the Overall Safety Population of subjects 6-59 months. Denominators for subjects 6-35 months: Afluria QIV n=694; Comparator QIV n=233; Overall n=927. Denominators for subjects 36-59 months: Afluria QIV n=979; Comparator QIV n=326; Overall n=1305.

***Afluria QIV recipient #(b) (6) had two SAEs: croup infectious and dehydration. All other subjects in the table had one SAE each.
Bold type indicates MedDRA system organ class (SOC). Bullets indicate MedDRA preferred term (PT).

Reviewer comment: Overall, SAEs were low in frequency and most were common diagnoses in a pediatric population 6-59 months of age. No large imbalances were observed between treatment groups.

Table 21 lists the 15 SAEs experienced by 14 subjects during the study according to treatment and age group, subject ID, onset, severity, and attribution. None of the SAEs were considered related to study vaccine by the investigators.

Table 21: SAEs Day 1 through Day 180 by Treatment, Age Group, and Subject (Overall Safety Population) – CSLCT-QIV-15-03*

Treatment Group	Age Group	Subject	Preferred Term	Onset[1]	Severity Grade[2]	Related[3]	Outcome
Afluria QIV	6-35 m	(b) (6)	Dysphagia	18	Grade 2	No	Resolved
Afluria QIV	6-35 m		Croup infectious	24	Grade 3	No	Resolved
Afluria QIV	6-35 m		Croup infectious	80	Grade 3	No	Resolved
Afluria QIV	6-35 m		Pneumonia respiratory syncytial viral	93	Grade 3	No	Resolved
Afluria QIV	6-35 m		Respiratory syncytial virus bronchiolitis	79	Grade 3	No	Resolved
Afluria QIV	6-35 m		Respiratory syncytial virus infection	7	Grade 3	No	Resolved
Afluria QIV	6-35 m		Animal bite	43	Grade 3	No	Resolved
Afluria QIV	6-35 m		Foreign body aspiration	56	Grade 2	No	Resolved
Afluria QIV	6-35 m		Dehydration	23	Grade 3	No	Resolved
Afluria QIV	6-35 m		Febrile convulsion	104	Grade 1	No	Resolved
Afluria QIV	6-35 m		Febrile convulsion	43	Grade 3	No	Resolved
Afluria QIV	6-35 m		Pneumonitis	41	Grade 3	No	Resolved
Comparator QIV	6-35 m		Impaired gastric emptying	178	Grade 3	No	Resolved
Comparator QIV	6-35 m		Bronchiolitis	29	Grade 3	No	Resolved
Comparator QIV	36-59 m		Humerus fracture	83	Grade 3	No	Resolved

Source: Adapted from STN 125254/692, Module 5, CSLCT-QIV-15-03 CSR, Tables 12.3-2, 14.3.1.10.1.1, 14.3.1.10.1.2, and 14.3.1.10.1.3, case narratives, and the electronic datasets.
*ClinicalTrials.gov identifier: NCT02914275.
[1]Onset = Number of days following most recent study vaccination (i.e., last dose) until onset of SAE.
[2]Severity Grade: 1=mild; 2=moderate; 3=severe.
[3]Related: "Yes" signifies investigator assessment of "related" to study vaccine. "No" signifies investigator assessment of "not related" to study vaccine. Applicant concurred with investigator assessments.

Case narratives and case report forms (CRFs) for each SAE were reviewed.
Three SAEs of interest (all in Afluria QIV recipients) are briefly summarized below, two cases of febrile seizures and a case of respiratory syncytial virus (RSV) infection resulting in hospitalization seven days post-vaccination.

- Subject #(b) (6) was an 18-month-old African American female with a history of chronic otitis media (December 2015-September 2016), mild eczema (September 2015-September 2016), bilateral pressure equalization tube insertion ((b) (6)), and rhinorrhea ((b) (6)). She previously received influenza vaccine on (b) (6) without complications. She received a single vaccination with 0.25 mL of Afluria QIV in the anterolateral thigh on (b) (6). On (b) (6), 43 days post-vaccination, she presented to an emergency department (ED) with a two week history of nasal congestion, and cough, and new onset of fever to 101.7°F. While in the waiting

room, she became unresponsive and was observed to have upper extremity and body jerking that resolved without treatment after 4-5 minutes. Rectal temperature was 104.4°F. She was treated with acetaminophen and ibuprofen and discharged with a diagnosis of simple febrile seizure due to upper respiratory infection. No imaging or blood work was recommended. Outcome was recovered. The investigator assessed the event as severe, serious, but not related to study vaccine due to lack of a close temporal relationship and the presence of a viral infection as an alternative cause of the fever and febrile seizure. The Applicant concurred with the investigator's assessment.

- Subject #(b) (6) was a 32-month-old female with a history of lactose intolerance and previous influenza vaccinations on (b) (6) and on an unspecified date prior to July 2016. She received a single dose of Afluria QIV on (b) (6) and on (b) (6), 104 days post-vaccination, experienced a febrile seizure. She was evaluated in an emergency room, had a temperature of 99.9°F, was treated with intravenous fluid, acetaminophen, and ibuprofen, discharged, and recovered on the same day. No specific contributory factors were identified. The investigator and Applicant assessed the event as mild, serious, and not related to study vaccine due to an implausible temporal relationship.
- Subject #(b) (6) was a 16-month-old female with no relevant medical history who last received influenza vaccination in December 2015. She received Afluria QIV, 0.25 mL, on (b) (6) and (b) (6). On (b) (6) she experienced symptoms of viral infection (cough, congestion, and rhinorrhea) assessed as severe, and on (b) (6), 7 days after the second vaccination, was hospitalized with uncontrolled fever and hypoxemia. Evaluation included a PCR positive for RSV. Chest x-ray was negative for pneumonia. She was discharged with a diagnosis of RSV and bronchiolitis. The investigator assessed the event as severe, serious, and not related to study vaccine due to an alternative plausible explanation for fever and respiratory symptoms. The Applicant concurred with the investigator's assessment.

Reviewer comment: Case narratives and case report forms (CRFs) for each SAE were reviewed. The reviewer agrees with the Applicant and investigator assessments that none of the 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.

Subpopulation Analyses of Serious Adverse Events

Subpopulation analyses of SAEs through Day 180 in Afluria QIV recipients revealed higher proportions of SAEs in children 6-35 months (0.7%) vs 36-59 months (none), whites (0.6%) vs blacks/African Americans (0.1%), and non-Hispanic/Latinos (0.6%) vs Hispanic/Latinos (0.1%). Rates of SAEs in males and females were 0.3% and 0.4%, respectively. SAEs were not reported among other racial groups.

Reviewer comment: Subpopulation analyses of SAEs according to age, race and ethnicity revealed a trend towards more SAEs in younger, white, and non-Hispanic/Latino recipients of Afluria as compared to older, black/African American, and Hispanic/Latino recipients. However, the very small number of SAEs overall precluded meaningful interpretation of these data.

6.1.12.5 Adverse Events of Special Interest (AESI)

Two AESIs, both febrile convulsions, were reported during the study. Both events occurred in recipients of Afluria QIV (Subjects #(b) (6)) and were serious but assessed as not related to study vaccine. Please see Section 6.1.12.4 for case summaries and Section 6.1.7 for the definition and monitoring plan for AESIs. Evaluation of the electronic datasets confirmed the Applicant's report.

6.1.12.6 Clinical Test Results

Clinical safety laboratories were not collected systematically in this study. Any laboratory or vital sign abnormalities obtained in the evaluation of serious, severe, or otherwise significant AEs are described in Sections 6.1.12.3 and 6.1.12.4. Evaluation of electronic datasets revealed no episodes of hypotension or anaphylaxis in the 30 minutes post-vaccination.

6.1.12.7 Dropouts and/or Discontinuations

Overall, 93.0% and 92.5% of Afluria QIV and Comparator QIV recipients completed the study, and 99.3% (both groups) provided at least some evaluable safety follow-up data. None of the total 7.1% of subject discontinuations were due to adverse events. The discontinuation rate was relatively low, similar between treatment groups, and was not likely to have significantly impacted the interpretation of safety results.

6.1.13 Study Summary and Conclusions

Immunogenicity Conclusions

Vaccination with Afluria QIV elicited an immune response that met the eight co-primary endpoints and pre-specified non-inferiority criteria for HI GMT ratios and SCR differences for all four vaccine virus strains contained in the vaccine as compared to a U.S.-licensed comparator QIV containing the same virus strains in a pediatric population 6 through 59 months.

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 36-59 months than 6-35 months for all four vaccine strains. For the A/H1N1 and A/H3N2 virus antigens, Afluria QIV met immune response criteria commonly used to evaluate influenza vaccines, i.e., that the LB of the 95% CI for the post-vaccination % HI titer ≥1:40 is at least 70% and, for the SCR, at least 40%, in subjects 6 through 59 months, overall and within each age cohort. Immune responses to the B virus strains were notably lower in both age cohorts, especially in subjects 6 through 35 months and for the B/Yamagata antigen. Afluria QIV met immune response criteria only for the SCR for B/Victoria in the younger age cohort, and met criteria for the SCRs but not for the % HI ≥1:40 for either of the B strains in the older age cohort. Immune responses in subjects who received Comparator QIV followed the same pattern, and, despite low responses to the B strains, Afluria QIV demonstrated non-inferior immunogenicity relative to the comparator. 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.

Subgroup analyses showed that post-vaccination GMTs, percentages of subjects with HI titers ≥1:40, and SCRs were similar between sexes in each treatment group. Post-vaccination GMTs in blacks/African American recipients of Afluria QIV trended higher as compared to whites for the A/H1N1 and A/H3N2 strains included in the vaccines. However, post-vaccination GMTs for the B strains and post-vaccination % HI ≥1:40 and SCRs for all four vaccine virus strains were generally similar between the two racial subgroups. The clinical significance of these observations is unknown and is 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. Post-vaccination GMTs, % HI ≥1:40, and SCRs were generally similar between Hispanic/Latino and non-Hispanic/Latinos recipients of Afluria QIV for the four vaccine strains included in the vaccines. SCRs for the A/H3N2 and B/Victoria antigens trended lower in Hispanic/Latino recipients than in non-Hispanic/Latino recipients of Afluria QIV. Overall, subanalyses of immune responses by sex, race, and ethnicity followed the patterns observed in the overall Per Protocol Population.

Safety Conclusions

Safety data following administration of Afluria QIV to healthy subjects 6 through 59 months suggested no serious concerns and were generally comparable to a U.S.-licensed QIV.

The most common AEs following any vaccination with Afluria QIV in subjects 6-35 months were injection site pain (20.8%) and redness (20.8%), irritability (32.9%), diarrhea (24.4%), and loss of appetite (20.0%), and, in subjects 35-59 months, injection site pain (35.5%) and redness (22.4%), malaise/fatigue (14.3%), diarrhea (12.1%), and myalgia (9.9%). Most events were mild to moderate in severity and <2 days in duration. Among subjects who received two doses, rates of solicited AEs were generally lower following the second dose. Rates of solicited AEs were generally similar between treatment groups. Severe reactogenicity was uncommon with slightly lower rates of any severe solicited local injection site AEs observed among Afluria QIV as compared to Comparator QIV recipients (6-35 months 0.7% vs 2.7% and 36-59 months 2.7% vs 5.7%, respectively) but similar rates of any severe solicited systemic AEs (6-35 months 3.1% vs 4.0% and 36-59 months 2.0% vs 1.6%, respectively).

Among subjects 6-35 months in the 7 days following any vaccination, fever ≥99.5°F axillary occurred in 7.2% and 11.9%, and severe fever ≥101.3°F axillary in 2.5% and 2.6% of Afluria QIV and Comparator QIV recipients, respectively. Among subjects 36-59 months in the 7 days following any vaccination, fever ≥99.5°F axillary occurred in 4.8% and 6.0%, and severe fever ≥101.3°F axillary in 1.2% and 0.9% of Afluria QIV and Comparator QIV recipients, respectively. No febrile seizures occurred in the 7 days following vaccinations.

No subjects died or were discontinued due to AEs in the six months post-vaccinations. SAEs were uncommon (Afluria QIV 0.7%, Comparator QIV 0.5%). Eleven of a total 15 SAEs occurred >28 days post-vaccination. All appeared unrelated to study vaccines. Non-serious unsolicited AEs occurred with similar frequencies and severity (mostly mild) between treatment groups.

Overall, rates of solicited local and systemic AEs in both age strata (6-59 months), including fever and severe AEs, in recipients of Afluria QIV were acceptable without unusual patterns or safety concerns. Consistent with conclusions from Seqirus' scientific

investigation of the root cause of febrile seizures and febrile events associated with the SH 2010 formulation of Afluria, the (b) (4) the four Afluria QIV vaccine virus strains used in study CSLCT-QIV-15-03 was associated with less pyrogenicity relative to historical rates. Postmarketing surveillance following approval will determine whether safety and reactogenicity data following administration of Afluria QIV observed in this study are generalizable to a broader pediatric population 6-59 months or to future vaccine formulations containing different antigens.

Overall, subpopulation analyses of Afluria QIV recipients showed similar rates of solicited AEs by sex, and trends towards lower rates of solicited local and systemic AEs in blacks/African Americans and Hispanic/Latinos as compared to whites and non-Hispanic/Latinos, respectively. 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 demonstrate statistically significant differences between subpopulations using inferential statistics, we cannot draw firm conclusions from the observed trends.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

The application supporting licensure of Afluria QIV in the pediatric population 6 through 59 months consisted of one study; integrated analyses of efficacy are not applicable.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The application supporting licensure of Afluria QIV in the pediatric population 6 through 59 months consisted of one study; integrated analyses of safety are not applicable.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

This supplement contained no new data pertaining to human reproduction and pregnancy.

9.1.2 Use During Lactation

Please see Section 9.1.1.

9.1.3 Pediatric Use and PREA Considerations

Two Phase 3 pediatric postmarketing requirements (PMRs) were associated with approval of Afluria QIV on August 26, 2016. 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 second PMR

was CSLCT-QIV-13-03, submitted in the current supplement STN 125254/692, a prospective, Phase 3, randomized, observer-blind, comparator-controlled, multicenter trial to evaluate the immunogenicity and safety of Afluria QIV versus a U.S.-licensed quadrivalent inactivated influenza vaccine in children aged 6 months through 4 years. Timelines for the second PMR were:

- Final protocol submission: July 31, 2016
- Study completion date: June 30, 2017
- Final report submission: December 31, 2017

Submission of STN 125254/692 required a PeRC review because the supplement contained data from a pediatric assessment in response to the second PREA PMR. On April 18, 2018, the PeRC concurred with the review team's assessment that data from study CSLCT-QIV-15-03 support licensure of Afluria QIV in infants and children 6 through 59 months. With approval of the current efficacy supplement STN 125254/692, Seqirus will have fulfilled the second PMR.

9.1.4 Immunocompromised Patients

Information regarding the safety and effectiveness of Afluria QIV in immunocompromised individuals is not sufficient to support specific recommendations in this population.

9.1.5 Geriatric Use

Afluria Quadrivalent was approved for use in adults ≥18 years on August 26, 2016. Please see the clinical review of STN 125254/565 for information supporting licensure in adults ≥65 years.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Afluria QIV is approved for administration via the PharmaJet® Stratis® Needle-Free Injection System (jet injector) in adults 18-64 years based on a study that demonstrated non-inferior immunogenicity and acceptable safety following administration of Afluria (trivalent formulation) via the jet injector in that age group (please see STN 125254/511 for details). In the absence of data specific to the pediatric population, we will not extend approval of administration of Afluria QIV via the PJ Stratis device to persons 6 through 59 months with this supplement.

10. CONCLUSIONS

Immunogenicity and safety data from CSLCT-QIV-15-03 submitted to this efficacy supplement support traditional approval of Afluria QIV for use in children 6 through 59 months.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 22 presents Risk-Benefit Considerations relating to approval of Afluria QIV in children 6 through 59 months.

Table 22: Risk-Benefit Considerations Afluria Quadrivalent in Children 6 through 59 Months		
Decision Factor	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition	• Influenza causes annual epidemics affecting ~5-20% of the population. Due to frequent point mutations in viral envelope glycoproteins, the extent and severity of seasonal epidemics are variable and unpredictable. • In the U.S., annual influenza-associated respiratory and circulatory mortality rates ranged from 3,349 to 48,614 (average 23,607) from 1976-2007. Hospitalizations ranged from 55,000 to 431,000. More recently, the CDC estimated that influenza resulted in 9.2 million to 60.8 million illnesses, 140,000 to 710,000 hospitalizations, and 12,000 to 56,000 deaths annually since 2010. Complications disproportionately affect persons < 2 years and ≥65 years of age and persons with underlying cardiac, respiratory, metabolic, or immune compromising medical conditions. The CDC estimates that 80%-90% of all seasonal influenza-related deaths and 50%-70% of hospitalizations occur in persons ≥65 years. However, antigenic shifts (genetic reassortment) may cause pandemics that also result in significant mortality among healthy children and young adults. • Since 1985, two genetically distinct B virus lineages have co-circulated and comprise ~ 25% of isolates in the U.S. During the ten seasons from 2001-2002 through 2010-2011, prediction of which B lineage would predominate was correct for only five seasons, resulting in a mismatch between the vaccine and the circulating strain for 50% of the 10 year period. The CDC estimated that in a season where there is a B strain mismatch, the availability of a quadrivalent influenza vaccine could result in an annual reduction of 2,200-970,000 influenza cases, 14-8,200 hospitalizations, and 1-485 deaths.	• Influenza is a serious, sometimes life-threatening disease. Persons of all ages are at risk for significant morbidity and mortality. • Protection requires annual vaccination with a formulation containing virus strains predicted to circulate during each season. • Influenza B causes ~25% of the overall influenza disease burden. Deaths and hospitalizations due to complications of influenza B infection appear lower than for A/H3N2 but higher than for seasonal A/H1N1. Vaccine coverage of both B strains is particularly desirable in young children who experience severe disease and high mortality due to B strains (34% of 309 pediatric deaths reported to the CDC during the 2004-2008 season and 38% of 115 pediatric deaths reported during the 2010-2011 season were due to influenza B). In one autopsy series of patients who died from influenza B, 90% of 32 mostly healthy children had evidence of myocardial injury. • In 2013, the World Health Organization and VRBPAC recommended inclusion of a second influenza B antigen in quadrivalent influenza vaccines to provide coverage of both B lineages concurrently.
Unmet Medical Need	• Five antiviral agents are licensed in the U.S. for the treatment or prevention of influenza in persons with severe, complicated, or progressive disease, or at higher risk for complications. Two adamantane agents are active only against influenza A and are no longer recommended because of widespread resistance. Neuraminidase inhibitors are also limited by emergence of resistance (primarily to type A viruses) and adverse reactions. • Influenza vaccines licensed for use in the pediatric population 6 months through 17 years in the U.S. include: two trivalent (FluLaval and Fluzone) and three quadrivalent (Fluarix, FluLaval and Fluzone) inactivated influenza vaccines (TIV and QIV). Vaccines approved in older children include trivalent (Afluria, Fluarix, Fluviron, and Flucelvax) and quadrivalent (Afluria Quadrivalent and Flucelvax Quadrivalent) IIVs, and trivalent and quadrivalent live-attenuated influenza vaccines (LAIV3 and LAIV4) (FluMist and FluMist Quadrivalent). Not all licensed products are manufactured and distributed in any given influenza season. • Approximately (b) (4) doses of influenza vaccine were distributed in the U.S. in the 2017-2018 season. Influenza vaccine coverage rates are relatively stagnant and remain below the DHHS Healthy People 2020 targets of 80% in persons 6 months through 64 years	• Immunoprophylaxis is the preferred method of controlling influenza. The ACIP recommends annual influenza immunization for all persons ≥6 mos of age with no contraindications to vaccination. • Antivirals are important adjuncts for treatment and prevention of influenza but are not substitutes for vaccination. • Currently licensed influenza vaccines are effective against antigenically matched strains, and are well tolerated. When vaccine and circulating viruses are well-matched, vaccination with IIV is ~60% effective in preventing influenza illness.

	of age and 90% in persons ≥65 years of age. Although this does not appear to be due to a shortage of vaccine, the doses of vaccine distributed for the 2017-2018 influenza season are less than the population for whom the vaccine is indicated.	• Inclusion of both B lineages as part of a quadrivalent vaccine is likely to provide additional benefit in most seasons and to become the standard of care. • An additional licensed QIV will be beneficial given the transition from TIV to QIVs and coverage targets.
Clinical Benefit	• In a randomized, controlled trial of 2247 subjects 6 through 59 months, vaccination with Afluria QIV elicited an immune response that met pre-specified co-primary endpoints and success criteria for non-inferior HI GMT ratios and SCR differences for all four vaccine virus strains as compared to U.S.-licensed Comparator QIV. Analyses of secondary endpoints (post-vaccination GMTs, % HI titers ≥1:40, and SCRs) demonstrated similar immune responses between treatment and age groups. Similar to previous studies of Afluria (TIV and QIV) and other IIVs, immune responses to influenza A vaccine virus strains were higher than responses to B strains in both treatment groups. • Subgroup analyses of Afluria QIV recipients showed similar post-vaccination GMTs, % HI titers ≥1:40, and SCRs between sexes. Subgroup analyses by race and ethnicity also showed similar immune responses except for a trend (non-overlapping 95% CIs) towards higher post-vaccination GMTs for A/H1N1 and A/H3N2 in blacks/African Americans as compared to whites, and lower SCRs for A/H3N2 and B/Victoria in Hispanic/Latinos as compared to non-Hispanic/Latinos. • Clinical benefit was inferred from Afluria TIV, manufactured by the same process as QIV, and for which clinical efficacy has already been demonstrated in adults (STN 125254.259).	• Non-inferior immunogenicity was demonstrated in subjects 6-59 months in an appropriately designed immunogenicity trial. • Immunogenicity results suggest that Afluria QIV is likely to confer protection against influenza similar to Afluria TIV for the strains common to both vaccines, and additional protection against the alternate B strain as compared to the trivalent formulation. Because Afluria QIV is manufactured by the same process as Afluria TIV and has demonstrated non-inferior immunogenicity and comparable safely, a clinical endpoint study to confirm clinical benefit is not necessary. • Subgroup analyses showed that immune responses between sexes, blacks and whites, and Hispanic/Latinos and non-Hispanic/Latinos were generally similar with some differences as noted. The significance of these observations is limited by the relatively small sample sizes and descriptive nature of the analyses.
Risk	• The most common AEs following any vaccination with Afluria QIV in subjects 6-35 months were injection site pain (20.8%) and redness (20.8%), irritability (32.9%), diarrhea (24.4%), and loss of appetite (20.0%); and, in subjects 35-59 months, injection site pain (35.5%) and redness (22.4%), malaise/fatigue (14.3%), diarrhea (12.1%), and myalgia (9.9%). Most events were mild to moderate in severity and <2 days in duration. Among subjects who received two doses, rates of solicited AEs were generally lower following the second dose. Rates of solicited AEs were similar between treatment groups. Severe reactogenicity was uncommon with slightly lower rates of any severe solicited local injection site AEs observed among Afluria QIV as compared to Comparator QIV recipients (6-35 months 0.7% vs 2.7% and 36-59 months 2.7% vs 5.7%, respectively) but similar rates of any severe solicited systemic AEs (6-35 months 3.1% vs 4.0% and 36-59 months 2.0% vs 1.6%, respectively). • Among subjects 6-35 months in the 7 days following any vaccination, fever ≥99.5°F axillary occurred in 7.2% and 11.9%, and severe fever ≥101.3°F axillary in 2.5% and 2.6%,of Afluria QIV and Comparator QIV recipients, respectively. Among subjects 36-59 months in the 7 days following any vaccination, fever ≥99.5°F axillary occurred in 4.8% and 6.0%, and severe fever ≥101.3°F axillary in 1.2% and 0.9%,of Afluria QIV and Comparator QIV recipients, respectively. No febrile seizures occurred in the 7 days following vaccinations. Two unrelated febrile seizures occurred in Afluria QIV recipients (6-35 months age group) at 43 and 104 days post-vaccination. • No subjects died or were discontinued due to AEs in the six months post-vaccinations. SAEs were uncommon (Afluria QIV 0.7%, Comparator QIV 0.5%). Eleven of a total 15 SAEs occurred >28 days post-vaccination. All appeared unrelated to study vaccines. Non-serious unsolicited AEs occurred with similar frequencies and severity (mostly mild) between treatment groups.	• The safety profile of Afluria QIV was comparable to a U.S.-licensed QIV and clinically acceptable. • Among subjects 6-59 months, rates of fever in the 7 days following vaccination with Afluria QIV were lower than Comparator QIV and lower than historical rates for Afluria TIV. (b) (4) the four Afluria QIV vaccine virus strains used in study CSLCT-QIV-15-03 appear associated with less pyrogenicity. Based on Seqirus' scientific investigation, manufacturing modifications, and clinical study results, we anticipate but cannot be certain that the lower rates of fever observed in CSLCT-QIV-15-03 are generalizable to a broader population 6-59 months, or to future vaccine formulations containing different antigens. • Subpopulation analyses represent trends and do not allow definitive conclusions. • Available data for Afluria and Afluria QIV are insufficient to inform vaccine-associated risks for adverse pregnancy outcomes. However, inactivated influenza vaccines have a long history of safety and are recommended in pregnant females.

	• Subpopulation analyses showed similar rates of solicited AEs by sex, and trends towards lower rates of solicited local and systemic AEs in blacks/African Americans and Hispanic/Latinos as compared to whites and 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. • Safety was not evaluated in pregnant women or nursing mothers.	
Risk Management	• No vaccine-related febrile seizures or cellulitis-like reactions occurred among Afluria QIV recipients in the clinical trial. Any potential for increased local or systemic reactogenicity, including febrile reactions, can be further described in postmarketing surveillance. • No new or unexpected safety signals were apparent in subjects 6-59 months. Therefore, the clinical review team and OBE/DE determined that a neither a safety PMR, REMS, nor a Black Box warning are required for Afluria QIV.	• The Applicant continually monitors clinical and postmarketing data for febrile seizures, extensive injection site swelling, and cellulitis-like reactions following Afluria TIV and QIV. • Risk management can be adequately addressed by describing the known safety profile of Afluria QIV in the PI and through routine postmarketing surveillance.

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11.2 Risk-Benefit Summary and Assessment

Afluria TIV has demonstrated clinical efficacy in adults 18-49 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 trivalent 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 IIVs. 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 6-59 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 SH 2010 formulation of Afluria, the (b) (4) 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 appears sufficient and will help clarify whether the lower rates of fever observed in CSLCT-QIV-15-03 are generalizable to a broader population 6-59 months or to future vaccine formulations containing different antigens.

11.3 Discussion of Regulatory Options

The Applicant has requested and the data support extending traditional approval of Afluria QIV to persons 6 months and older. Please see Section 11.1.

11.4 Recommendations on Regulatory Actions

From the clinical perspective, data from CSLCT-QIV-15-03 support traditional approval of Afluria QIV in children 6 through 59 months. 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. Please see Section 11.1 for further discussion.

11.5 Labeling Review and Recommendations

Labeling negotiations were ongoing at the time the clinical review was finalized. Major changes to the Applicant's draft new Afluria QIV PI and areas of negotiation were as follows:

- Highlights, Indications and Usage [1], and Dosage and Administration [2]: Updated with an indication for use in persons 6 through 59 months, a new dosage of 0.25 mL for persons 6 through 35 months, and a dosing regimen of

one or two doses at least one month apart for persons 6 through 59 months as indicated based on prior vaccination history.

- Highlights and Adverse Reactions [6.1]: Added safety data from CSLCT-QIV-15-03 in persons 6 through 59 months.
- Highlights, Pregnancy [8.1], and Patient Counseling Information [17]: Updated with contact information for the pregnancy registry.
- Pediatric Use [8.4]: Based on a sound scientific investigation into the root cause of the SH 2010 febrile adverse events, modifications to the manufacturing process and testing, and subsequent clinical studies demonstrating rates of fever similar to comparator IIVs, the review team concurred with the Applicant's proposal to remove the description of the SH 2010 febrile events from Section 8.4 of the PI. Please see Section 4.1, CMC issues, for additional discussion.
- Clinical Studies [14]: Added immunogenicity data from CSLCT-QIV-15-03 in persons 6-59 months.

As part of the Afluria Quadrivalent sBLA, the Applicant requested licensure of Afluria (trivalent formulation) in persons 6 through 59 months, based on the quadrivalent study data, and submitted a draft new PI for Afluria (STN 125254/692.3). Major changes to the Afluria PI and areas of negotiation were as follows:

- Highlights, Indications and Usage [1], and Dosage and Administration [2]: Updated with an indication for use in persons 6 through 59 months, a new dosage of 0.25 mL for persons 6 through 35 months, and a dosing regimen of one or two doses at least one month apart for persons 6 through 59 months as indicated based on prior vaccination history.
- Highlights and Warnings and Precautions [5]: Removed the warning of increased postmarketing reports of fever and febrile seizures, predominantly in children <5 years, associated with the SH 2010 formulation of Afluria.
- Highlights and Adverse Reactions [6.1]: Added safety data from CSLCT-QIV-15-03 (Afluria Quadrivalent) in persons 6 through 59 months to support approval of the trivalent formulation in this population. Recommended against the Applicant's proposal to replace safety data for the trivalent formulation of Afluria in persons 5-17 years (currently in the PI) with safety data from CSLCT-QIV-15-02 (Afluria Quadrivalent) in persons 5-17 years because the trivalent data remain relevant and were the basis of approval in this population.
- Use in Pregnancy [8.1] and Lactation [8.3]: Updated for consistency with the Pregnancy and Lactation Labeling Rule (PLLR).
- Pediatric Use [8.4]: Removal of the description of the SH 2010 febrile seizures and febrile events, consistent with revisions to the Afluria Quadrivalent PI.
- Clinical Studies [14]: Added immunogenicity data from CSLCT-QIV-15-03 (Afluria Quadrivalent) in persons 6 through 59 months to support approval of the trivalent formulation in this population. Recommended against the Applicant's proposal to replace immunogenicity data for the trivalent formulation of Afluria in persons 5-17 years (currently in the PI) with immunogenicity data from CSLCT-QIV-15-02 (Afluria Quadrivalent) in persons 5-17 years because the trivalent data remain relevant and were the basis of approval in this population.

Please refer to the final version of the PIs, available in the EDR.

11.6 Recommendations on Postmarketing Actions

The review team recommended no additional PMCs or PMRs beyond those outlined in the August 26, 2016 Approval Letter for Afluria Quadrivalent. The pediatric PMRs are fulfilled with this supplement. The pregnancy registry is ongoing. Please see Sections 1, Executive Summary, and 9.1.3, Pediatric Use and PREA Considerations, and the OBE/DE review for details.