BLA Clinical Review Memorandum

Application Type	Efficacy Supplement
STN	125254.642
CBER Received Date	October 31, 2016
PDUFA Goal Date	August 31, 2017
Division / Office	DVRPA/OVRR
Priority Review	No
Reviewer Name	Cynthia Nolletti, MD
Review Completion Date / Stamped Date	April 21, 2017 August 28, 2017
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
Formulation	Each 0.5mL dose contains 15µg hemagglutinin (HA), total 60µg, from each of the recommended influenza types and subtypes: • A/H1N1 • A/H3N2 • B/Yamagata • 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 0.5 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 0.5 mL doses (based on prior vaccination history) IM ≥1 month apart by needle-syringe (persons 5 years 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 ≥5 years.
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
FDAAA	Food and Drug Administration Amendments Act of 2007
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
ITT	intent-to-treat
JI	jet injector
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
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
SP	Safety Population
(b) (4)	(b) (4)
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

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 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 a given season. The dosage of Afluria QIV in adults is 60 mcg [15 mcg per hemagglutinin (HA) antigen] administered intramuscularly (IM).

Afluria TIV was granted accelerated approval in the U.S. in children and adolescents 6 months through 17 years 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 comparator. FDA subsequently, on July 15, 2011, restricted the indication for Afluria TIV to children and adolescents ≥5 years. Rates of fever (100.4°F) and severe fever (≥102.2°F) following Afluria TIV from pooled clinical trial data in children 5 through 8 years were 13.93% and 3.32%, respectively.

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) could reduce the induction of pro-inflammatory cytokines in vitro, and Seqirus hypothesized that (b) (4)

(b) (4) might reduce the pyrogenicity of Afluria in children. The formulation of Afluria QIV used in the pediatric study of subjects 5 through 17 (CSLCT-QIV-13-02) submitted to this sBLA used the (b) (4) (b) (4) all four vaccine virus antigens.

Seqirus submitted data from a single study, CSLCT-QIV-13-02, to support the safety and effectiveness of Afluria QIV in a pediatric population 5 through 17 years. CSLCT-QIV-13-02 was a prospective, phase 3, observer-blind, comparator-controlled, multicenter study conducted in the U.S. during the Northern Hemisphere (NH) 2015-2016 influenza season in 2278 generally healthy children and adolescents 5 through 17 years, stratified approximately equally into two age cohorts (5 through 8 years and 9 through 17 years), and randomized 3:1 to receive Afluria QIV or a U.S.-licensed 2015-2016 comparator quadrivalent inactivated influenza vaccine (Fluarix Quadrivalent, GlaxoSmithKline Biologicals, referred to as "Comparator QIV" in this review). Subjects 9 through 17 years received a single 60 mcg dose while subjects 5 through 8 years received one or two doses administered ~28 days apart based on their previous influenza vaccination history in accordance with 2015-2016 recommendations by the Advisory Committee for Immunization Practices (ACIP). 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. The non-inferiority (NI) analyses and success criteria used in this study are recommended by CBER and are typically used in the evaluation of effectiveness of influenza vaccines by immunogenicity. 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, defined as concurrent Grade 3 (severe) injection site pain, induration/swelling and redness, were monitored for 28 days following each vaccination. Subjects were instructed to contact the study site and attend an additional clinic visit within 24 hours of onset of a cellulitis-like reaction for evaluation by a clinician. 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 were also asked to attend an additional clinic visit within 72 hours of onset for evaluation of an influenza-like illness (ILI) occurring within 28 days of vaccination.

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 5 through 17 years. Secondary objectives were to assess the safety and tolerability of Afluria QIV, and to further characterize the immunogenicity of Afluria QIV compared to a U.S.-licensed QIV among children 5 through 17 years in two age strata: 5 through 8 years and 9 through 17 years.

CSLCT-QIV-13-02 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. 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. Non-inferior immunogenicity of

Afluria QIV as compared to Comparator QIV 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 safety endpoints, evaluated among children 5-8 years, 9-17 years, and overall, included the frequency and severity of: solicited injection site reactions and systemic adverse events in the seven days after each vaccination; unsolicited AEs in the 28 days post-vaccinations; cellulitis-like reactions at the injection site in the 28 days post-vaccinations; and SAEs in the 180 days post-vaccinations.

Exploratory analyses of immunogenicity and safety included subpopulation analyses 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 2133 subjects 5 through 17 years, of whom 1605 received Afluria QIV and 528 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 5 through 17 Years (Per Protocol Population) – CSLCT-QIV-13-02*

Strain	GMT[1] Afluria QIV (n=1605)[6]	GMT[1] Comparator QIV (n=528)	GMT[1,2] Ratio (95% CI)	SCR[3] Afluria QIV (n=1605) (95% CI)	SCR[3] Comparator QIV (n=528) (95% CI)	SCR[4] Difference (95% CI)	Met NI Criteria?[5]
A/H1N1	952.6	958.8	1.01 (0.93, 1.09)	66.4 (64.0, 68.7)	63.3 (59.0, 67.4)	-3.1 (-8.0, 1.8)	Yes
A/H3N2	886.4	930.6	1.05 (0.96, 1.15)	82.9 (81.0, 84.7)	83.3 (79.9, 86.4)	0.4 (-4.5, 5.3)	Yes
B/Yamagata	60.9	54.3	0.89 (0.81, 0.98)	58.5 (56.0, 60.9)	55.1 (50.8, 59.4)	-3.4 (-8.3, 1.5)	Yes
B/Victoria	145.0	133.4	0.92 (0.83, 1.02)	72.1 (69.8, 74.3)	70.1 (66.0, 74.0)	-2.0 (-6.9, 2.9)	Yes

Source: STN 125254/642, Module 5, CSLCT-QIV-13-02 CSR, Tables 11.4-1, 14.2.1.1, and 14.2.2.1
*ClinicalTrials.gov identifier: NCT02545543
Abbreviations: A/H1N1=A/California/7/2009 (H1N1) pdm09-like virus; A/H3N2=A/Switzerland/9715293/2013 (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.
[1]GMTs adjusted for covariates: treatment group, age subgroup, sex, vaccination history, pre-vaccination GMT, 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 8400394-0046 was excluded from the PPP for the adjusted GMT analysis for the GMT ratio because the subject did not have information on all covariates (i.e., unknown previous vaccination history).

Analyses of secondary immunogenicity endpoints, pre- and post-vaccination GMTs, post-vaccination % HI ≥1:40, and SCRs showed that immune responses were similar between Afluria QIV and Comparator QIV, overall and within each age cohort. Statistically significantly lower pre- and post-vaccination HI GMTs and % HI ≥1:40 were observed for the B virus strains relative to the A strains, and may reflect lower rates of prior wild type or vaccine exposure to influenza B antigens, especially in the younger age cohort. However, a pattern of lower responses to B strains is not unusual for influenza vaccines, and Afluria QIV demonstrated non-inferior immunogenicity relative to the comparator.

Summary of Safety

The Overall Safety Population (OSP) was used to summarize all safety data, and included all randomized subjects 5 through 17 years 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 2,252 subjects, including 1692 and 560 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 4.7%, Comparator QIV 6.0%) were due to AEs.

In the 180 days following any vaccination, a total of 10 subjects, 8 (0.5%) Afluria QIV and 2 (0.4%) Comparator QIV recipients, reported 13 SAEs. Six of 8 Afluria QIV recipients and both Comparator QIV recipients who reported SAEs were in the 9-17 year age stratum. Most SAEs occurred >28 days post-vaccination and were not unusual diagnoses in a pediatric and adolescent population. With the exception of a case of influenza B infection that may be considered a vaccine failure and in that context related, 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.

The Solicited Safety Population (SSP) was used to summarize 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 events. Of a total 1103 subjects 5 through 8 years (Afluria QIV n=829, Comparator QIV n=274) in the SSP, 57.2% and 54.0% of Afluria QIV and Comparator QIV recipients, respectively, reported solicited local reactions, primarily pain (51.3% vs 49.6%, respectively), followed by redness (19.4% vs 18.6%) and swelling (15.3% vs 12.4%, respectively). Most reactions were mild to moderate in severity. Severe local reactions occurred in 5.5% and 4.0% of Afluria QIV and Comparator QIV recipients, respectively. Although rates of local reactions were generally similar between treatment groups, there was a small imbalance

in the overall rate of local swelling between Afluria QIV and Comparator QIV recipients (as noted) and in the rates of severe local swelling (3.4% vs 2.2%, respectively) and severe redness (3.5% vs 1.8%, respectively), with more Afluria QIV recipients reporting severe reactogenicity. The mean onset of all local reactions in subjects 5 through 8 years 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. Among subjects 5 through 8 years who received two vaccinations (Afluria QIV n=178, Comparator QIV n=63), rates of all local reactions and severe reactions were lower following the second dose, although the difference in overall rates of local swelling following the second vaccination was smaller with Afluria QIV (Dose 1 = 14.0%, Dose 2 = 11.2%) relative to Comparator QIV (Dose 1 = 12.5%, Dose 2 = 4.8%).

Among 1053 subjects 9 through 17 years (Afluria QIV n=792, Comparator QIV n=261) in the SSP, 54.9% and 50.2% of Afluria QIV and Comparator QIV recipients, respectively, reported solicited local reactions, primarily pain (51.5% vs 45.2%, respectively), followed by redness (14.8% vs 16.1%, respectively) and swelling (12.2% vs 10.7%, respectively). Most reactions were mild in severity. The overall rates of any severe local reaction were similar between treatment groups (Afluria QIV 3.2%, Comparator QIV 3.8%). The mean onset (Day 1 to Day 2) and duration (1.5 to 2.0 days) of local reactions were also similar between treatment groups.

The trivalent formulation of Afluria was associated with increased reports of local cellulitis-type reactions primarily during the 2011 Southern Hemisphere season. For that reason, combined with concerns for a potential increase in local reactogenicity with the addition of a second B strain antigen, the occurrence of cellulitis-like reactions (concurrent Grade 3 injection site pain, induration/swelling and redness) in the SSP during the 28 days following vaccination was a pre-specified study endpoint. During this period, one 8-year old recipient of Afluria QIV (and no Comparator QIV recipients) had a non-serious cellulitis-like reaction with accompanying moderately severe systemic AEs. All events resolved with treatment within 11 days of vaccination.

Among 1103 subjects 5 through 8 years in the SSP, 27.6% and 26.3% of Afluria QIV and Comparator QIV recipients, respectively, reported solicited systemic AEs. The most frequently reported symptoms among Afluria QIV and Comparator QIV recipients, respectively, were headache (12.3% vs 10.6%), myalgia (9.8% vs 11.3%), malaise/fatigue (8.8% vs 5.8%), and nausea (7.1% vs 8.4%). Fever was uncommon, however, rates of any fever (≥100.4°F) among Afluria QIV recipients were slightly higher than Comparator QIV recipients (4.5% vs 3.6%, respectively) as were rates of severe (Grade 3) fever (≥102.2°F or ≥39.0°C) (1.2% vs 0.7%). Most events were mild to moderate in severity with a total of 1.6% and 1.5% of Afluria QIV and Comparator QIV recipients, respectively, reporting severe systemic AEs (predominantly fever). Mean onset (Day 2 to Day 4) and mean duration (<2 days) of solicited systemic AEs were similar between treatment groups. Mean onset of fever was on Day 3 in both treatment groups, with similar durations of 1.2 to 1.3 days. Among subjects 5-8 years who received two vaccinations, rates of solicited systemic AEs following the second vaccination were lower than the first vaccination in both treatment groups. Fever occurred in 4.0% and 3.0% of Afluria QIV and Comparator QIV recipients, respectively, after the first vaccination and in 2.2% and 3.2%, respectively, after the second vaccination. No subjects in either treatment group reported severe solicited systemic AEs, including fever, following the second vaccination. No febrile seizures were reported.

Among 1053 subjects 9 through 17 years in the SSP, 34.1% and 28.7% of Afluria QIV and Comparator QIV recipients, respectively, experienced solicited systemic AEs. The most frequently reported events occurred at higher rates in Afluria QIV recipients relative to Comparator QIV: headache (18.8% vs 14.6%), myalgia (16.7% vs 11.1%), and malaise/fatigue (10.0% vs 7.7%). Fever was uncommon but a small imbalance was observed between treatment groups, 2.1% vs 0.8% of Afluria QIV and Comparator QIV recipients, respectively. Severe solicited systemic AEs were uncommon, occurring in 1.4% and 0.8% of Afluria QIV and Comparator QIV, respectively. Severe (Grade 3) fever (≥102.2°F or ≥39.0°C) occurred in 0.5% of Afluria QIV recipients and in none of the comparator recipients. Mean onset (range Day 1.7 to Day 4.0) of solicited systemic AEs was similar between treatment groups. Most events resolved within two days.

A total of 310 subjects (13.8%) 5 through 17 years reported 503 unsolicited AEs in the 28 days following vaccination(s), with a slighter higher proportion of Afluria QIV recipients (14.4%) reporting unsolicited AEs as compared to Comparator QIV (12.0%), and higher overall rates of AEs among subjects 5-8 years (Afluria 16.2%; Comparator 15.0%) as compared to subjects 9-17 years (Afluria 12.5%; Comparator 8.8%) in both treatment groups. Among Afluria QIV recipients, the largest disparities in rates of AEs in subjects 5-8 years vs 9-17 years, respectively, as categorized by SOC between age strata were: Infections and Infestations (5.7% vs 3.6%); Respiratory, Thoracic, and Mediastinal Disorders (4.7% vs 3.4%); and General Disorders and Administration Site Conditions (4.3% vs 1.9%). Among Comparator QIV recipients, a similar trend towards higher rates of AEs in subjects 5-8 years as compared to 9-17 years was observed in these same SOC categories. Within body system categories, frequencies of individual events were low and generally similar between treatment groups. Among recipients of Afluria QIV 5 through 8 years, the most common unsolicited AEs (frequency ≥1%) were: cough (2.4%), pyrexia (1.8%), rhinorrhea (1.2%), and headache (1.0%). Among recipients of Afluria QIV 9 through 17 years, the most common unsolicited AEs were: oropharyngeal pain (1.6%), cough (1.3%), and upper respiratory tract infection (1.0%). Most events were mild to moderate in severity and appeared unrelated to study vaccine. Overall, no clinically significant vaccine-related large imbalances or unusual patterns were observed between age and treatment groups.

Overall, the frequency, severity, and duration of local and systemic solicited and unsolicited AEs following vaccination with Afluria QIV in study CSLCT-QIV-13-02 were acceptable and not unusual for an inactivated influenza vaccine. Small imbalances in the rates of severe injection site reactions, fever, and other solicited systemic symptoms indicate that Afluria QIV was slightly more reactogenic than the comparator in the study population. However, the imbalances did not appear clinically significant because overall rates were low and no events were serious. No febrile seizures were reported. In particular, rates of fever in Afluria QIV recipients 5 through 8 years were lower than historical rates for Afluria (trivalent formulation) in this age group. 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) (b) (4) the four Afluria QIV vaccine virus strains used in study CSLCT-QIV-13-02 was associated with less pyrogenicity. Postmarketing surveillance following approval may help determine whether the slightly higher but acceptable rates of local and systemic reactogenicity observed following administration of Afluria QIV in this study are generalizable to a broader pediatric population 5-17 years and to future vaccine formulations containing different antigens.

The Package Insert (PI) will describe the case of cellulitis-like reaction in Section 6.1, Clinical Trials Experience, and "cellulitis and large injection site swelling" in Section 6.2, Postmarketing Experience. The PI describes the association between the SH 2010 trivalent formulation of Afluria and febrile seizures and other febrile AEs in Section 8.4, Pediatric Use.

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.

Submission of STN 125254/642 required a PeRC review because the supplement contained data from a PREA PMR. On April 5, 2017, the PeRC concurred with the review team's assessment that data from CSLCT-QIV-13-02 support licensure of Afluria QIV in children and adolescents 5 through 17 years. With approval of the current efficacy supplement STN 125254/642, Seqirus will fulfill the PMR to conduct a phase 3 study to evaluate the immunogenicity and safety of Afluria QIV in a pediatric population 5 years through 17 years. Timelines for the outstanding PREA PMR in infants and children 6 months through 4 years, according to the August 26, 2016 Approval Letter, are as follows:

- Final Protocol Submission: July 31, 2016 (completed)
- Study Completion Date: June 30, 2017
- Final Report Submission: December 31, 2017

Pharmacovigilance Plan – 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). OBE/DE does not recommend 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. The clinical review team agreed with the OBE/DE recommendation. 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-13-02 support a recommendation for traditional approval of Afluria QIV in the pediatric population 5 years through 17 years 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 2278 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. Overall, there were more male (52.1%) than female (47.9%) subjects. The majority of subjects were white (73.3%) and non-Hispanic or Latino (76.0%). Black/African American and Hispanic/Latino subjects comprised 20.7% and 23.8% of the FAS, respectively. American Indian/Alaskan Native (0.3%), Asian (0.8%), Native Hawaiian/Pacific Islander (0.7%), and racial groups identified as "other" (4.3%) comprised the remainder of the FAS. Demographic and baseline characteristics within each age cohort were similar to the FAS and between treatment groups. Relative to the U.S. population, blacks/African Americans and Hispanics/Latinos were overrepresented, and Asians were underrepresented.

The mean age (SD) of all subjects in the FAS was 9.5 (3.48) years; 6.7 (1.10) for the 5-8 year age cohort; and 12.5 (2.52) for the 9-17 year age cohort. As specified by the protocol, at least 50% of subjects in the FAS (51.2%) were in the 5-8 years cohort.

Subpopulation Analyses of Immunogenicity
Subgroup analyses showed that post-vaccination GMTs, % HI ≥1:40, and SCRs were similar between sexes in each treatment group and age cohort. Subgroup analyses of these 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. Subanalyses showed a statistically significant trend (non-overlapping 95% CIs) towards higher post-vaccination GMTs for A/H1N1 and A/H3N2 in black as compared to white recipients of Afluria QIV and non-statistically significant (overlapping 95% CIs) lower SCRs in Hispanic/Latinos as compared to non-Hispanic/Latinos. Immune responses were otherwise similar between sex, race and ethnic groups. Subanalyses of non-inferiority for Afluria QIV relative to Comparator QIV showed that GMT ratios and SCR differences between sexes, blacks and whites, and Hispanic/Latinos and non-Hispanic/Latinos were not statistically significantly different. The clinical significance of these observations is uncertain 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
Rates of deaths and SAEs in CSLCT-QIV-13-02 were too low to perform meaningful subpopulation analyses.

Subpopulation analyses of solicited AEs among Afluria QIV recipients showed a trend toward slightly higher rates of injection site pain and swelling and headache in females as compared to males, and slightly higher rates of fever in males relative to females.

Overall, in the pediatric population 5-17 years, a total of 54.7% and 57.5% male and female recipients of Afluria QIV, respectively, experienced solicited local injection site reactions. A total of 29.9% and 31.7% of male and female recipients of Afluria QIV, respectively, experienced solicited systemic AEs. Differences between males and females, respectively, in rates of solicited local and systemic AEs were as follows: pain 49.0% vs 53.9%; redness 16.6% vs 17.8%; swelling 12.8% vs 14.8%; fever 4.1% vs 2.5%; headache 14.6% vs 16.4%; myalgia 13.7% vs 12.6%; malaise/fatigue 9.0% vs 9.8%; nausea 7.6% vs 7.2%; diarrhea 5.2% vs 5.5; and vomiting 2.2% vs 2.0%.

Subpopulation analyses showed that blacks/African Americans reported less local and systemic reactogenicity as compared to whites following vaccination with Afluria QIV. Among the pediatric population 5-17 years, 45.7% and 59.0% of black/African American and white recipients of Afluria QIV, respectively, experienced solicited local injection site reactions, and 22.6% and 33.6%, respectively, experienced solicited systemic AEs. Differences in rates of specific local reactions and systemic symptoms between blacks/African Americans and whites, respectively, were as follows: pain 42.7% vs 53.7%; redness 7.3% vs 19.9%; swelling 12.2% vs 14.0%; fever 3.4% vs 3.3%; headache 10.1% vs 17.1%; myalgia 10.1% vs 14.4%; malaise/fatigue 5.2% vs 10.8%; nausea 5.2% vs 8.2%; diarrhea 3.4% vs 5.9%; and vomiting 3.0% vs 2.0%.

Overall, Hispanic/Latinos reported less solicited local reactions and systemic symptoms than non-Hispanic/Latinos following vaccination with Afluria QIV. Among the pediatric population 5-17 years, 45.4% and 59.5% of Hispanic/Latino and non-Hispanic/Latino recipients of Afluria QIV, respectively, experienced solicited local reactions, and 25.0% and 32.6%, respectively, experienced solicited systemic AEs. Differences in rates of solicited local reactions and systemic symptoms between Hispanic/Latinos and non-Hispanic/Latinos, respectively, were as follows: pain 41.0% vs 54.7%; redness 9.8% vs 19.4%; swelling 9.0% vs 15.4%; fever 1.3% vs 4.0%; myalgia 10.8% vs %13.8; headache 10.1% vs 17.2%; malaise/fatigue 7.7% vs 9.9%; nausea 4.1% vs 8.5%; diarrhea 3.6% vs 5.9%; and vomiting 1.5% vs 2.3%.

Reviewer comment: Subpopulation analyses of Afluria QIV recipients showed trends towards more local reactogenicity in females as compared to males, and more local and systemic reactogenicity in whites and non-Hispanic/Latinos as compared to blacks/African Americans and Hispanic/Latinos, respectively. However, the observations represent trends and do now allow firm conclusions. Small sample sizes precluded meaningful analyses of racial subgroups other than blacks and whites.

Overall rates of unsolicited AEs in the 28 days following vaccination in Afluria QIV recipients 5-17 years were similar between males (14.8%) and females (13.9%). No large differences between males and females were observed in the rates of AEs as categorized by body system or individual event terms.

Sub-analyses of racial groups revealed a trend towards lower overall rates of unsolicited AEs in blacks/African American as compared to white recipients of Afluria QIV (11.7% vs 15.3%, respectively). The largest disparities in rates of AEs between blacks/African Americans and whites, respectively, were observed in the SOC categories of Infections and Infestations (2.9% vs 5.3%) and General Disorders and Administration Site Conditions (2.3% vs 3.4%). Small sample sizes precluded meaningful sub-analyses of other racial groups.

Overall rates of unsolicited AEs among Afluria QIV recipients were lower in Hispanic/Latinos as compared to non-Hispanic/Latinos (10.6% vs 15.6%). The greatest differences between Hispanic/Latinos and non-Hispanic/Latinos, respectively, occurred in the following SOCs: Infections and Infestations (2.7% vs 5.3%); Respiratory, Thoracic, and Mediastinal Disorders (3.4% vs 4.3%); and General Disorders and Administration Site Conditions (1.5% vs 3.7%).

Reviewer comment: Overall, subpopulation analyses showed trends towards higher rates of unsolicited AEs in whites and non-Hispanic/Latino recipients of Afluria QIV as compared to blacks/African Americans and Hispanic/Latinos, and no clear trends observed between sexes. Because the study was not designed to detect statistically significant differences between subpopulations, 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 indication has since been extended to persons 5 years and older. Dosage of the trivalent formulation in adults is 45 µg [15 µg of HA antigen per virus strain] administered IM. 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. In this efficacy supplement, the Applicant has submitted safety and immunogenicity data to support extension of the indication for Afluria QIV to persons 5 through 17 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, 140,000 to 710,000 hospitalizations, and 12,000 to 56,000 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. [6,10,11,12,13,14,16,17,23,31,33]

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 influenza surface antigens 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. [11,12,31,47,54]

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 a season 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 those attributed to 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, six 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. [5,14,16,40,54,57]

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. Antigenic variants or strain changes occur each year necessitating annual change 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.[11,12,27,31,33,34,37]

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.[11,14,17]

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 chemoprophylaxis of influenza in persons ≥ 5 years of age and for treatment in persons ≥ 7 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 and newest NA inhibitor, peramivir, is a single dose intravenous antiviral indicated only for the treatment of uncomplicated influenza A and B viral infection in persons 18 years of age and older. Adverse events include diarrhea, serious cutaneous reactions and postmarketing reports of neuropsychiatric events. Due to concerns for potential emergence of resistance and side effects, NA inhibitors are considered important adjuncts but not substitutes for vaccination. [13,15,17,24,31]

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 quadrivalent live-attenuated influenza vaccine (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 a given influenza season. Six IIV3 [Afluria (5 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 four IIV4

[Fluarix Quadrivalent (3 years 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. LAIV4 (FluMist Quadrivalent) is currently approved for use only in healthy non-pregnant persons 2 to 49 years of age. One IIV4 (Fluzone Intradermal) is 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 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. A meta-analysis of RCTs of IIVs (primarily in healthy adults) reported a pooled efficacy of 59% (95% CI: 51%, 67%) in preventing laboratory-confirmed influenza. One randomized controlled trial 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%). 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)].
[11,15,16,17,18,19,21,22,25,26,28,31,32,33,36,38,39,42,43,44,46,47,49,50,51,53,55,56,58,61,62,66]

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 randomized controlled trials, often occur at rates similar to those observed in placebo recipients making causality uncertain. [16,31,35,59,65]

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).
[16,31,35,41,59,65]

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

Afluria QIV was initially approved for use in adults ≥18 years in the U.S. 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 regarding the clinical trial experience from CSLCT-QIV-13-01. There is no previous human experience with Afluria (Seqirus) QIV in the pediatric population. At the time this efficacy supplement was

submitted, Seqirus QIV had not been licensed by any other regulatory authority, and no postmarketing experience was available in any population. 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). The manufacturing process has not changed since 1985 except for eliminating the preservative, thimerosal, from single use presentations in 2002. Therefore, 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. 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. Data from CSLCT-QIV-13-02, 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 5 through 8 Years* and 9 through 17 Years

Age Group Study Treatment	**N**	**Dose 1 Any Fever ≥100.4°F % (95% CI)**	**Dose 1 Fever ≥102.2°F % (95%CI)**	**Dose 2 Any Fever ≥100.4°F % (95%CI)**	**Dose 2 Fever ≥102.2°F % (95%CI)**	**Strains** (b) (4) [redacted]
5-8 years CSLCT-FLU-04-05 (SH 2005) Afluria TIV	Dose 1 n=82 Dose 2 n=82	9.76 (4.31,18.32)	2.44 (0.30,8.53)	1.22 (0.03,6.61)	1.22 (0.03,6.61)	None
5-8 years CSLCT-USF-06-29 (SH 2009) Afluria TIV	Dose 1 n=511 Dose 2 n=339	13.89 (11.01,17.20)	2.94 (1.65,4.80)	7.37 (4.83,10.69)	2.06 (0.83,4.21)	None
5-8 years CSLCT-USF-07-36 (NH 2009-2010) Afluria TIV	Dose 1 n=161 Dose 2 n=39	16.15 (10.83,22.76)	4.97 (2.17,9.56)	0.00 (n/a,9.03)	0.00 (n/a,9.03)	None
5-8 years Pooled** Afluria TIV	Dose 1 n=754 Dose 2 n=460	13.93 (11.53,16.6)	3.32 (2.16,4.86)	5.65 (3.73,8.17)	1.74 (0.75,3.40)	None
5-8 years CSLCT-USF-07-36 Fluzone TIV	Dose 1 n=165 Dose 2 n=53	8.48 (4.72,13.83)	1.21 (0.15,4.31)	1.89 (0.05,10.07)	0.00 (n/a,6.72)	n/a***
5-8 years CSLCT-USF-10-69 Afluria TIV	Dose 1 n=292 Dose 2 n=120	8.22 (5.34,11.98)	2.05% (0.76,4.42)	0.00 (n/a,3.03)	0.00 (n/a,3.03)	A/H3N2 B/Yamagata
5-8 years CSLCT-USF-10-69 Fluzone QIV	Dose 1 n=98 Dose 2 n=39	8.16 (3.59,15.45)	3.06 (0.64,8.69)	5.13 (0.63,17.32)	5.13 (0.63,17.32)	n/a***
5-8 years CSLCT-QIV-13-02	Dose 1 n=826 Dose 2 n=178	4.00 (2.77,5.57)	1.21 (0.58,2.22)	2.25 (0.62,5.65)	0.00 (n/a,2.05)	A/H1N1 A/H3N2

Age Group Study Treatment	**N**	**Dose 1 Any Fever ≥100.4°F % (95% CI)**	**Dose 1 Fever ≥102.2°F % (95%CI)**	**Dose 2 Any Fever ≥100.4°F % (95%CI)**	**Dose 2 Fever ≥102.2°F % (95%CI)**	**Strains** (b) (4)
Afluria QIV						B/Yamagata B/Victoria
5-8 years CSLCT-QIV-13-02 Flurix QIV	Dose 1 n=271 Dose 2 n=63	2.95 (1.28,5.73)	0.74 (0.09,2.64)	3.17 (0.39,11.00)	0.00 (n/a,5.69)	n/a***
9-17 years CSLCT-USF-06-29 Afluria TIV	Dose 1 n=397	5.04 (3.10,7.67)	1.01 (0.28,2.56)	n/a	n/a	None
9-17 years CSLCT-USF-07-36 Afluria TIV	Dose 1 n=254	6.30 (3.64,10.03)	3.15 (1.37,6.11)	n/a	n/a	None
9-17 years Pooled** Afluria TIV	Dose 1 n=651	5.53 (3.90,7.57)	1.84 (0.96,3.20)	n/a	n/a	None
9-17 years CSLST-USF-07-36 Fluzone TIV	Dose 1 n=250	4.00 (1.93,7.23)	0.80 (0.10,2.86)	n/a	n/a	n/a***
9-17 years CSLCT-QIV-13-02 Afluria QIV	Dose 1 n=792	2.15 (1.26,3.41)	0.51 (0.14,1.29)	n/a	n/a	A/H1N1 A/H3N2 B/Yamagata B/Victoria
9-17 years CSLCT-QIV-13-02 Flurix QIV	Dose 1 n=261	0.77 (0.09,2.74)	0.00 n/a,1.40)	n/a	n/a	n/a***

Source: STN 125254/642.4, Module 5, CSLCT-QIV-13-02 CSR, Table 1.11.3-1
Abbreviations: (b) (4) ; TIV=trivalent inactivated influenza vaccine; QIV=quadrivalent inactivated influenza vaccine; SH=Southern Hemisphere; NH=(Northern Hemisphere).
*Analyses of children 5 through 8 years in studies CSLCT-FLU-04-05, CSLCT-USF-06-29, and CSLCT-USF-07-36 represent post-hoc subanalyses.
**Pooled studies: CSLCT-FLU-04-05, CSLCT-USF-06-29, and CSLCT-USF-07-36 for 5-8 year age group; CSLCT-USF-06-29 and CSLCT-USF-07-36 for 9-17 year age group.
***Comparator vaccine virus strains are (b) (4) .

Reviewer comment: Clinical trial data from earlier studies of Afluria TIV [CSLCT-FLU-04-05 (SH 2005), CSLCT-USF-06-29 (SH 2009), and CSLCT-USF-07-36 (NH 2009-2010)] suggest that Afluria was more pyrogenic than other TIVs even prior to the SH 2010 increased postmarketing reports of febrile seizures and febrile events, particularly in the youngest age group 6 through 59 months (data not shown) but also in the younger age group of children 5-8 years as compared to 9-17 years. Rates of fever following the first vaccination with Afluria TIV or Fluzone TIV in children 5-8 years in CSLCT-USF-07-36 were 16.15% and 8.48%, respectively, and, for fever ≥102.2°F, 4.97% and 1.21%, respectively. Rates of fever in subjects 9-17 years from earlier studies of Afluria TIV were also higher than for Fluzone TIV (CSLCT-USF-07-36) but the difference between treatment groups was much less, sample sizes were smaller, and confidence intervals on point estimates overlapped to a greater degree.

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 facilitated 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) ,

(b) (4) . 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 an (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 Seqirus TIV pediatric studies, 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) .

Reviewer comment: Limitations of study CSLCT-USF-10-69 included historical comparisons, post hoc analyses, and small sample sizes. Additionally, although rates of fever were not increased in recipients of Afluria TIV relative to Comparator QIV in this study, the potential effect of adding another antigen (the second B strain) to Afluria TIV on the pyrogenicity of the QIV formulation in the pediatric population was still unknown. A further concern was one SAE (one in 300 recipients of Afluria in this study) of fever and delirium that occurred in a 7-year old male two days following vaccination with Afluria TIV, raising some concerns over whether the modified formulation was sufficiently less pyrogenic. Therefore, the Applicant designed CSLCT-QIV-13-02 with stringent halting rules and, at our request, required a Data Safety Monitoring Board (DSMB) review of 7-day safety data from a sentinel group of children 5 through 8 years of age prior to enrolling the remainder of the age cohort.

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

The original sponsor of CSLCT-QIV-13-02 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 sponsor of the study.

- 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.
- April 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 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.
- 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 for discussion of the rates of fever observed in study CSLCT-USF-10-69 as compared to earlier studies that used (b) (4) Afluria.
- 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 of the PSP.
- August 15, 2014 – STN 125254/511. CBER approved bioCSL's supplement to support the safety and efficacy of administration of Afluria by the PharmaJet® Stratis® Needle-Free Injection System (a jet injector) in persons 18 through 64 years.
- April 21, 2015 – A pre-BLA 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). The protocol for CSLCT-QIV-13-02 was subsequently submitted to IND 15974/24.

- February 10, 2016 – The PeRC concurred with the final PSP submitted to STN 125254/565. Please see Section 9.1.3 for details of the PSP.
- 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, a draft PI, and a pregnancy registry for Afluria QIV. Please see meeting summary for details (CRMTS #10232, IND 15974/32).
- August 26, 2016 – Afluria QIV was approved in adults ≥18 years (STN 125254/565). Approval included administration of Afluria QIV intramuscularly either by needle and syringe or, in adults 18 through 64 years only, via the PharmaJet® Stratis® Needle-Free Injection System.

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 without unreasonable difficulty.

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, federal regulations, and local ethical and regulatory requirements. These requirements included IRB approval of the protocol and the informed consent of parents/guardians and pediatric assent where required by the IRB.

Bioresearch Monitoring (BIMO), Division of Inspections and Surveillance, Office of Compliance and Biologics Quality, conducted an inspection of five clinical study sites (316, 384, 395, 396, and 397). Inspections found no deficiencies that would preclude approval. Please see the BIMO review for details.

3.3 Financial Disclosures

The Applicant provided a signed Form FDA 3454 and a list of investigators for the clinical study submitted to this 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. Please see the CMC review for details.

4.2 Assay Validation

The hemagglutination inhibition (HI) assay and reverse transcriptase polymerase chain reaction (rtPCR) were performed by (b) (4)
USA. The CMC reviewer identified no significant deficiencies in regard to the HI assay validation data submitted to the sBLA. Please see the DVP review 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 validated 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. Other antibodies, e.g., to NA, nuclear protein (NP), and/or M1 protein, and cellular responses to vaccination may contribute to protection. [11,12,27,29,31,33,34,37,45,56]

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 had identified no issues that would preclude approval of the supplement.

4.6 Pharmacovigilance

Please see the OBE/DE review of the Pharmacovigilance Plan (PVP).

- The OBE/DE reviewer 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.
- OBE/DE noted that the relative risk (RR) of injection site swelling among Afluria QIV recipients was slighter higher as compared to IIV4 in study CSLCT-QIV-13-02 [RR 1.23 (95% CI 0.87, 1.76) among subjects 5-8 years and 1.14 (95% CI 0.77, 1.70) among subjects 9-17 years]. Additionally, because a case of cellulitis-like reaction following administration of Afluria QIV in CSLCT-QIV-13-02, OBE/DE asked the Applicant to explain why “large/extensive injection site swelling” and “cellulitis-like reactions” were listed as important potential risks rather than important identified risks in the updated version of the PVP. The Applicant responded that, because only one subject in Afluria QIV clinical trials

experienced a cellulitis-like reaction, no subjects reported extensive limb swelling similar to the postmarketing reports of 2011, and rates of moderate and severe solicited injection site redness/erythema and swelling/induration were similar between Afluria QIV and comparator QIV recipients, they have concluded that extensive injection site swelling and cellulitis-like reactions remain important potential but not identified risks (STN 125254/642.7). While OBE/DE continues to regard these events as important identified risks, they noted that there are no regulatory definitions for these risk categories or requirements that the sponsor agree with our assessment. "Cellulitis and large injection site swelling" will remain in Section 6.2 of the PI and the different assessments of potential versus identified risks will not alter the plan for routine pharmacovigilence.

- ODE/DE calculated slighter higher relative risks of solicited fever (all grades) among Afluria QIV recipients in each of the two age groups: RRs of 1.22 (95% CI: 0.62, 2.43) among subjects 5-8 years and 2.80 (95% CI: 0.65, 12.04) among subjects 9-17 years. The reviewer concluded that the occurrence of fever following vaccination was comparable between treatment groups but that fever continues to be an event of interest and warrants close monitoring in postmarketing surveillance.
- The Applicant agreed to establish a pregnancy registry for Afluria QIV during the pre-sBLA meeting, and submitted a pregnancy registry protocol to this supplement (125254/642.2 and 125254/642.10). Please see the OBE/DE review for details and comments.

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

5.1 Review Strategy

Seqirus conducted one pivotal study, CSLCT-QIV-13-02, to support licensure of Afluria QIV in children and adolescents 5 through 17 years. 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-13-02 were similar to those which supported licensure of Afluria (TIV) and of Afluria QIV in adults ≥18 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.

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

- STN 125254/642.0 – Modules 1, 2 and 5, and associated electronic datasets.
- STN 125254.642.1 – Response to 12/5/16 information request (IR), case narratives for pregnancies, severe cellulitis, severe fever, case report forms (CRFs) for SAEs, ILI confirmation.
- STN 125254.642.2 – Response to 12/9/16 IR regarding ADAE datasets, onset of AEs relative to dose, definitions of Analysis Flags.
- STN 125254.642.3 – Responses to 12/5/16 IR (items 5 and 6), subpopulation analyses of NI and covariate analyses.
- STN 125254.642.4 – Responses to 12/16/16 IR. Clarification of cases of fever categorized as unsolicited rather than solicited AEs, definitions for AECAT categories, request for tabular summary of historical fever rates.

- STN 125254/642.5 – Revised unsolicited AE tables summarizing unsolicited AEs from Day 1 through 28 days after the final vaccination instead of through 180 days after the final vaccination as originally submitted in the CSR.
- STN 125254/642.7 – Response to OBE/DE IR (dated 3/15/17) regarding categorization of cellulitis and large injection site swelling.
- STN 125254/642.10 – Pregnancy registry protocol.
- Labeling amendments: STN 125254/642.6; STN 125254/642.8, STN 125254/642.12; STN 125254/642.13.

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 5 through 17 years.

Table 3: Summary of Clinical Trials Submitted to STN 125254/642

Study ID NCT# Season Location	Design	Population Enrolled*	Objectives	Endpoints**	Analysis Populations
CSLCT-QIV-13-02 NCT 02545543 NH 2015-2016 USA	Phase 3, observer-blind, comparator-controlled, multicenter study, stratified by age (5-8 and 9-17 years), randomized 3:1 to receive one or two 0.5mL doses administered IM 28 days apart (depending on vaccination history) of Afluria QIV or U.S.-licensed Comparator QIV. 0.5 mL dose = 15 mcg HA per strain	Healthy persons 5-17 years 2278 Total 1709 Afluria QIV 569 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: 2252 Total; 1692 Afluria QIV; 560 Comparator QIV Per Protocol 2133 Total; 1605 Afluria QIV; 528 Comparator QIV

Source: Adapted from STN 125254/642, Module 5, CSLCT-QIV-13-02 CSR text and Tables 2.5.4-2 and 14.1.1.1.
NCT=ClinicalTrials.gov identifier; NH=Northern Hemisphere; IM=intramuscular; QIV=quadrivalent influenza vaccine; Comparator QIV=Fluarix 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 College of Obstetricians and Gynecologists Frequently Asked Questions: Miscarriage and Molar Pregnancy; 2011.

2Atmar RL, et al. Influenza vaccination of patients receiving statins: Where do we go from here? J Infect Dis 2016;213:1211-1213.

3Avalos LA, et al. A systematic review to calculate background miscarriage rates using life table analysis. Birth Defects Research 2012;94:417-423.

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20Centers 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.

21Centers 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).

22Centers 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

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24Centers 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 .

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

"A Phase 3, Randomized, Multicenter, Observer-Blinded, Non-inferiority Study to Evaluate the Immunogenicity and Safety of bioCSL Quadrivalent Inactivated Influenza Virus Vaccine (bioCSL QIV) with a US-Licensed 2015-2016 Quadrivalent Inactivated Comparator Influenza Vaccine (Comparator QIV) in a Pediatric Population 5 through 17 Years of Age".

6.1.1 Objectives

Primary Objective
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, among a pediatric population 5 through 17 years of age.

Secondary Objectives

- To assess safety and tolerability of Afluria QIV among children 5 through 17 years of age in two age strata: 5 through 8 and 9 through 17 years, as well as overall.
- To characterize the immunogenicity of Afluria QIV and the U.S.-licensed comparator QIV in two age strata: 5 through 8 and 9 through 17 years, as well as overall.

Exploratory Objectives

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

6.1.2 Design Overview

CSLCT-QIV-13-02 was a phase 3, randomized, observer-blinded, comparator-controlled, multicenter study of Afluria QIV versus U.S.-licensed 2015-2016 comparator QIV containing the same influenza strains recommended by the VRBPAC for the NH 2015-2016 influenza season. The study was conducted in the NH 2015-2016 influenza season in male and female subjects (planned n=2222) 5 through 17 years, stratified into two age cohorts, 5 through 8 (Cohort A) and 9 through 17 (Cohort B) years, using a quota to ensure that at least 50% of subjects were enrolled in Cohort A. Eligibility criteria allowed enrollment of generally healthy children and adolescents but permitted medically stable common co-morbid conditions (see Section 6.1.3). After stratification, subjects were randomized 3:1 to receive either Afluria QIV or Comparator QIV in a regimen of one or two vaccinations 28 days apart depending on age and prior vaccination history and as recommended by the ACIP for the 2015-2016 influenza season. Accordingly, children 5 years through 8 years who previously received at least two total doses of TIV or QIV before July 1, 2015 (not necessarily in the same or consecutive seasons) were eligible for one dose, while children in this age group who had not received a total of two doses of TIV or QIV before July 1, 2015 were eligible for two doses.

Following parental or guardian informed consent and subject assent (age appropriate for 7-11 and 12-17 years), subjects were screened for eligibility within a maximum of 7 days prior to intramuscular (IM) administration of the first study vaccination on Day 1. Blood samples for HI antibody titers were collected prior to the first and 29 days (+4) after the last study vaccinations. Parents or guardians recorded solicited local and systemic symptoms and temperature for 7 days (Day 1 through Day 7), and unsolicited AEs for 28 days, following each vaccination in electronic diaries. Cellulitis-like reactions, defined as concurrent Grade 3 injection site pain, erythema, and induration, were also 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 contact 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. Criteria for an ILI were an oral temperature of ≥100.4°F (≥38.0°C) (or clear history of fever or chills), and at least one influenza-like symptom (including sore throat, cough, myalgia, headache, malaise, rhinitis, otitis media, nausea, and vomiting).

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 April 21, 2015 followed by submission of a study protocol (IND 15974/24). The comparator QIV was required by FDA to be a U.S.-licensed inactivated quadrivalent influenza vaccine and was selected by the Applicant 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 at least 50% of subjects to the 5 through 8 year 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 (observer blind). 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-13-02 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). During review of STN 125254/565 (Afluria QIV in adults ≥18 years), the review team discussed adding these two adverse events to the Adverse Events of Special Interest (AESIs) described in the Applicant's formal Pharmacovigilance Plan (PVP). OBE/DE recommended adding these AEs to the PVP as "important potential risks", and a request was sent to the Applicant. Accordingly, Seqirus has added these AEs as "important potential risks" in the updated PVP (Edition 2.0, 13 September 2016). For further discussion of this issue, please see Section 4.6.

6.1.3 Population

Selected Inclusion Criteria

- Males or females 5 through 17 years 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. Participant assent obtained if 7 through 17 years and required by the IRB.
- Females of childbearing potential (ovulating and not surgically sterile) must be abstinent or willing to use medically acceptable contraception until at least 28

days after last study vaccine (see CSR Module 5, Section 9.3.1, p.57 for acceptable contraceptive methods), and must have a negative urine pregnancy test immediately prior to vaccination(s).

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 oral temperature ≥100°F (37.8°C) within 48 hours of vaccination.
- 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 seizures, 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, inhaled or localized tissue injections of corticosteroids prior to vaccination or throughout the study were acceptable.
- Receipt of or plans to receive live or inactivated licensed vaccine within 28 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.
- History of drug or alcohol abuse within the previous 12 months.
- Pregnant or lactating females.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Both study vaccines were inactivated split virion quadrivalent influenza vaccines. A single 0.5 mL dose of each vaccine contained 15 mcg of HA antigen for each of the 4 strains recommended by FDA's VRBPAC for the NH 2015-2016 influenza season (total HA = 60 mcg). Both vaccines were supplied as thimerosal-free suspensions in needleless pre-filled syringes, and were administered intramuscularly (IM) into the deltoid region of the arm, either as a single 0.5 mL dose or as two 0.5 mL doses 28 days apart depending on age and previous vaccination history.

The four influenza strains recommended by FDA's VRBPAC for the NH 2015-2016 season quadrivalent vaccines were:

- A/California/7/2009 (H1N1)pdm09-like virus
- A/Switzerland/9715293/2013 (H3N2)-like virus
- B/Phuket/3073/2013-like virus (B/Yamagata lineage)
- B/Brisbane/60/2008-like virus (B/Victoria lineage)

Afluria QIV
Lot Number: 090403401

U.S.-Licensed Comparator QIV (Fluarix Quadrivalent, GlaxoSmithKline Biologicals)
Lot Number: 4A5K3

6.1.5 Directions for Use

Not applicable.

6.1.6 Sites and Centers

CSLCT-QIV-13-02 was conducted at 32 centers across the U.S. Study sites and the principal investigator for each site are presented in Table 4.

Table 4: Study Sites, Investigators, and Number of Subjects* - CSLCT-QIV-13-02**

Site	Investigator	Location	#Subjects*
282	William Seger, MD	Fort Worth, TX	90
283	Laurence Chu, MD	Austin, TX	79
285	Frank Eder, MD	Binghamton, NY	81
287	Larkin Wadsworth, MD	St. Louis, MO	67
288	Darrell Herrington, DO	San Angelo, TX	95
289	Mark Turner, MD	Meridian, ID	117
293	Murray A. Kimmel, DO	Melbourne, FL	58
294	Daniel H. Brune, MD	Peoria, IL	49
296	Randle T. Middleton, MD	Huntsville, AL	43
300	Derek Muse, MD	Salt Lake City, UT	75
316	James A. Cervantes, MD	Bellevue, NE	74
317	Terry L. Poling, MD	Wichita, KS	84
382	James Wax, MD	Omaha, NE	63
383	Holly Dushkin, MD	Cleveland, OH	84
384	Samir Arora, MD	Columbus, OH	83
385	Rajesh Davit, MD	Cincinnati, OH	49
386	Daniel Finn, MD	Bardstown, KY	77
387	David Horowitz, MD	Cary, NC	60
388	Daria Altamirano, DO	Hialeah, FL	56
389	Frank Calcagno, MD	Gresham, OR	64
390	Michael Rausch, MD	Agusta, KS	78
392	Thiruvoipati Nandakumar, MD	Redding, CA	52
393	George Bauer, Jr., MD	Metairie, LA	93
394	Douglas Denham, DO	San Antonio, TX	66
395	Nathan Forbush, MD	Layton, UT	85
396	Stacy Slechta, DO	Newton, KS	88
397	Rosario Retino, MD	Ontario, CA	82
398	Juan Carrillo, MD	San Jose, CA	50
399	Julie Shepard, MD	Dayton, OH	78
400	James Kahrs, MD	Park City, KS	74
401	Aftab Naz, MD	Madera, CA	45
402	William Douglas, MD	Sacramento, CA	39

Source: Adapted from STN 125254.642, CSLCT-QIV-13-02 CSR, Appendix 16.1.4 and electronic datasets.
*Number of subjects in the Full Analysis Set.
**ClinicalTrials.gov identifier: NCT02545543

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-13-02***

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 +/- assent	X[1]	X	--	--	--	--	--	--
Baseline characteristics	X[1]	X	--	--	--	--	--	--
Medical history, meds	X[1]	X	--	--	--	--	--	--
Targeted physical exam	X[1]	X	--	X	--	X**	--	--
Oral temperature	--	X	--	X**	--	--	--	--
Urine pregnancy test[2]	--	X	--	X	--	X**	--	--
Eligibility criteria	--	X	--	--	--	--	--	--
Serologies	--	X	--	X*	--	X**	--	--
Vaccination	--	X	--	X**	--		--	--
Solicited Diary review	--	--	X	X	X**	X**	--	--
Unsolicited/Concomitant Medications Diary review	--	--	X	X	X**	X**	--	--
Telephone contact	--	--	X	--	X**	--	X	X
Assess cellulitis-like reaction or ILI[3]	--	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-13-02 CSR, Tables 9.5-1 and 9.5-2, pp.68-69.
*Single dose subjects only.
**Two-dose subjects only.
***ClinicalTrials.gov identifier: NCT02545543
[1]Screening could be performed on the day of or up to 7 days prior to vaccination.
[2]Females of child-bearing potential only.
[3]If applicable, assess for cellulitis-like reaction (defined as concurrent Grade 3 injection site pain, erythema, and induration) or influenza-like illness (ILI) [defined as oral temperature ≥100.4°F (≥38.0°C) or a clear history of fever or chills, and at least one flu-like symptom (including sore throat, cough, wheezing, myalgia, headache, malaise, rhinitis, dyspnea, nausea, and vomiting). For ILI, collect nasal swabs from right and left nares and a throat swab.

Subjects who completed screening assessments and fulfilled eligibility criteria were enrolled. 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. Vaccination was postponed in the event of a febrile illness (oral temperature ≥100.0°F or ≥37.8°C) or prophylactic antipyretic use on the day of vaccination, and administered only after being afebrile for at least 48 hours and assessed by the investigator as recovered. Subjects were observed for immediate hypersensitivity reactions for at least 30 minutes after each vaccination.

Parents and guardians received instructions for completing the electronic solicited and unsolicited AE diaries, including a local injection site measurement card and a digital thermometer for taking subjects' oral temperature on the evening of vaccination and at the same time for the subsequent six days (i.e., Days 1 through Day 7). They were provided with two separate URL links to record AEs and medications electronically: a Solicited eDiary link and an Unsolicited/Concomitant Medications eDiary link. 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).

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. Study investigators/delegates were to perform additional clinical investigations as necessary to evaluate and manage the reaction.

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

- Elevated oral temperature of ≥100.4°F (≥38.0°C) (or a clear history of fever or chills), AND
- At least one flu-like symptom (including sore throat, cough, dyspnea, wheezing, myalgia, headache, malaise, rhinitis, nausea, and vomiting). 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.

Definitions and Criteria for the Assessment of Severity and Causality of AEs

Definitions of AEs and SAEs were consistent with those in 21 CFR 312.32. 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-13-02*

Solicited Local Reactogenicity	**Grade 0 (none)**	**Grade 1 (mild)**	**Grade 2 (moderate)**	**Grade 3 (severe)**
Pain	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	<100.4°F (<38.0°C)	≥100.4°F to <101.3°F (≥38.0°C to <38.5°C)	≥101.3°F to <102.2°F (≥38.5°C to <39.0°C)	≥102.2°F (≥39.0°C)
Headache Myalgia Malaise/Fatigue Nausea Vomiting Diarrhea	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	Discomfort sufficient to cause some interference with normal everyday	Symptoms prevent normal, everyday activities

Solicited Local Reactogenicity	Grade 0 (none)	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)
		activities	activities	

Source: Adapted from Module 5, CSLCT-QIV-13-02 CSR, Tables 9.5.3.4-1 and 9.5.3.4-2 and text, p.74.
*ClinicalTrials.gov identifier: NCT02545543
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:

- 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. Therefore, AESIs were recorded on the SAE page of the eCRF as meeting criteria for "medically significant" events and any other criteria as applicable.

Reviewer comment: These events 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. Please see Section 6.1.2, Design Overview, for further discussion of this issue.

Pregnancy

If a female subject or female partner of a male subject became pregnant during the study period, the protocol required reporting to Seqirus Safety within 5 working days of the investigator becoming aware. Pregnancies were followed to outcome, and the status of the mother and infant after delivery or premature termination reported by the investigator to Seqirus. Pregnancies were not considered SAEs unless they met criteria for seriousness (e.g., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly) in which case they were reported as such.

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 this assessment 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 Endpoint (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 as follows:

- GMT ratio for the A/H1N1 strain
- GMT ratio for the A/H3N2 strain
- GMT ratio for the B strain (Yamagata lineage)
- GMT ratio for the B strain (Victoria lineage)
- SCR difference for the A/H1N1 strain
- SCR difference for the A/H3N2 strain
- SCR difference for the B strain (Yamagata lineage)
- SCR difference for the B strain (Victoria lineage)

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%.

Secondary Endpoints (Immunogenicity)
The immunogenicity of Afluria QIV was further assessed in terms of HI antibodies for each of the four vaccine virus strains in the two age strata (5 through 8 years and 9 through 17 years) and overall (5 through 17 years). Serum HI antibodies measured pre-vaccination on Day 1 and post-vaccination (28 days after the final vaccination) were used to calculate:

- GMT: geometric mean of HI titers pre-vaccination and post-vaccination;
- SCR: defined as for the primary endpoint;
- The percentage of subjects with an HI titer ≥1:40 (% HI ≥1:40) at Day 1 and 28 days after the final vaccination;
- Geometric mean fold increase (GMFI) in GMT from Day 1 to 28 days after the final vaccination, where GMFI was defined as the geometric mean of the fold increases of the post-vaccination HI titer over the pre-vaccination HI titer.

Reviewer comment: The primary and secondary immunogenicity endpoints were appropriate. Regarding the secondary endpoints, because the GMFI is a criterion used by the European Medicines Agency (EMA) but not by CBER to assess the immunogenicity of influenza vaccines, this review will focus only on the secondary endpoints of GMT, SCR, and % HI ≥1:40. Please see the previous reviewer comment regarding study design in Section 6.1.2.

Secondary Endpoints (Safety)

The following endpoints were evaluated among children 5 through 8 years, 9 through 17 years, and overall:

- 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 Endpoints (Immunogenicity)

- GMTs, SCRs, and the % HI ≥1:40 were explored with adjustments for covariates including pre-vaccination HI titer, vaccination history, number of doses, age, and sex to evaluate the contribution of these variables to variations in the immune response.

Exploratory Endpoints (Safety)

- Outcomes of any fever and severe fever were explored for potential associations with age, sex, weight, vaccine dose, and previous influenza vaccination.

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-13-02 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 5 through 17 years. In mathematical notation, the statistical hypotheses for the primary immunogenicity analysis were:

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

and

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

where Ri was any of the four strain-specific Day 28 post-vaccination GMT ratios:

- (Comparator QIV) / (Afluria QIV) for B/Yamagata strain
- (Comparator QIV) / (Afluria QIV) for B/Victoria strain
- (Comparator QIV) / (Afluria QIV) for A/H1N1 strain
- (Comparator QIV) / (Afluria QIV) for A/H3N2 strain

and Di was any of the four strain-specific Day 28 post-vaccination SCR differences:

- (Comparator QIV) - (Afluria QIV) for B/Yamagata strain
- (Comparator QIV) - (Afluria QIV) for B/Victoria strain
- (Comparator QIV) - (Afluria QIV) for A/H1N1 strain

- (Comparator QIV) - (Afluria QIV) for A/H3N2 strain.

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.

For the primary immunogenicity analyses, the GMT ratio was adjusted for the following covariates: treatment group, age cohort (5-8 and 9-17 years), sex, influenza vaccination in the prior year, pre-vaccination GMT, number of dose (1 vs 2), and investigator site. Exploratory analyses of the primary endpoint were also performed with adjustment for individual covariates to evaluate the contribution of these factors to variation in the immune response.

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.

Sample Size

The sample size was calculated to provide at least 80% power to demonstrate non-inferiority for all 8 co-primary endpoints of SCRs and GMTs for each of the 4 vaccine virus strains using a one-sided alpha of 0.025 for each comparison in the overall study population 5 through 17 years. No adjustment was made for multiple endpoints. NI margins of 10% and 1.5 were employed for the SCR difference and GMT ratio, respectively. Assumptions included a SCR of 50% for all strains with no difference between Afluria QIV and Comparator QIV, and GMT ratios of 1.0, 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 89.70% power for the four SCR endpoints and 99.95% power for the four GMT ratio 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 (e.g., violations of eligibility criteria or failure to collect pre- or post-vaccination serologies). Minor deviations were those that did not have significant impact as defined above. 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 4].

Missing Data

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

Subjects for whom data was missing for all 7 days for solicited AEs were omitted from the denominator when calculating the rate for those events. If severity data was only

partially missing for the 7-day solicited AE period for an event, then the missing severity of 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. Study sites and the CRO remained blinded until the final database lock. The review team, including the statistical reviewer, agreed that this approach was acceptable during the April 21, 2015 meeting with the Applicant and review of the study protocol (IND 15974/24).

Changes in the Conduct of the Study or Planned Analyses
One amendment was made to the final protocol. The revisions were made prior to the first subject visit and included minor clarifications.

Changes made to the SAP were completed prior to the interim database lock on February 8, 2016 and unblinding, and included:

- Clarification in criteria to define whether a subject had any follow-up safety data
- A Solicited Safety Population was added to the analysis populations and used for the analysis of solicited AEs. This allowed a more conservative assessment of solicited AE rates because it eliminated subjects who had unsolicited AE follow-up data but no solicited AE data from the denominator.
- Safety tables not specified in the SAP were added: summary of all solicited and unsolicited AEs (Safety Population) to provide intensity data for solicited and unsolicited AEs overall; and related solicited systemic AEs overall and by maximum intensity for the total population and by age stratum.

The study database was locked on July 2, 2016 and was unlocked on September 22, 2016 to allow AE data to be updated for two subjects who had received Afluria QIV.

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

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 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. A statement that there were no

AEs constituted follow-up data provided that a follow-up safety visit or phone call had occurred.

- 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:
    - o received study vaccine at Visit 1;
    - o 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)];
    - o did not experience a laboratory-confirmed influenza illness between Visit 1 and the Exit Visit; and
    - o 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.
    - o 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 in the event that there was a > 1% difference in the total number of subjects in either of the two age strata (5-8 or 9-17 years) between the PPP and EP. Because the difference in the number of subjects between the EP and the PPP was 1.67% for the 5-8 year stratum, duplicate tables of primary immunogenicity analyses were provided based on the EP.

6.1.10.1.1 Demographics

Table 7 presents demographics 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 (52.1%, 73.3%, and 76.0%, respectively). The mean age (SD) of all subjects was 9.5 (3.48) years; 6.7 (1.10) for the 5-8 year age cohort; and 12.5 (2.52) for the 9-17 year age cohort. As specified by the protocol, at least 50% of subjects in the FAS were 5 through 8 years (51.2%).

Table 7: Demographics and Baseline Characteristics – CSLCT-QIV-13-02 (Full Analysis Set)*

Characteristic	**Afluria QIV N=1709**	**Comparator QIV N=569**	**Total N=2278**	**U.S. Census (2015)****
Mean Age (yrs) (SD)	9.5 (3.49)	9.5 (3.46)	9.5 (3.48)	--
Age Group %	--	--	--	--
5-8 yrs	51.2	51.1	51.2	--
9-17 yrs	48.8	48.9	48.8	--
Gender – Male, %	51.7	53.1	52.1	49.3

Characteristic	Afluria QIV N=1709	Comparator QIV N=569	Total N=2278	U.S. Census (2015)**
Gender – Female, %	48.3	46.9	47.9	50.7
Race, %	--	--	--	--
American Indian/Alaska Native	0.3	0.4	0.3	1.2
Asian	0.9	0.4	0.8	5.5
Black/African American	21.0	19.9	20.7	13.2
Native Hawaiian/Pacific Islander	0.8	0.4	0.7	0.2
White/Caucasian	72.5	75.6	73.3	77.3
Other	4.5	3.5	4.3	--
Ethnicity, %	--	--	--	--
Hispanic/Latino	24.1	22.8	23.8	17.7
Non-Hispanic/Latino	75.7	77.0	76.0	82.3

Source: Adapted from STN 125254/642, Module 5, CSLCT-QIV-13-02 CSR, Tables 11.2-1, 14.1.2.1, and 14.1.2.2
*ClinicalTrials.gov identifier: NCT 02545543
**Projections released by the U.S. Census Bureau in December 2014 based on the 2010 U.S. Census. Accessed on January 22, 2017 at http://www.census.gov/population/projections/data/national/2014/summarytables.html
Estimated total U.S. population=321,369,000. Persons 5 years through 17 years=53,670,000. Male=158,345,000. Female=163,024,000. 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.

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 U.S. population, blacks/African Americans and Hispanics/Latinos were overrepresented, and Asians were underrepresented. [64]

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Influenza Vaccination History

Of the 2278 subjects in the FAS, 1998 (87.7%) subjects reported ever having received an influenza vaccine including 53.0% in the 2014-2015 NH season during the 12 months prior to enrollment. The percentages of subjects who reported ever receiving influenza vaccination or in the NH 2014-2015 season were similar between age cohorts: 87.3% and 55.9%, respectively (5-8 years); 88.1% and 49.9%, respectively (9-17 years). The percentage of subjects 5-17 years who reported previous influenza vaccination was also similar between treatment groups (Afluria QIV 87.7%, Comparator QIV 87.9%).

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 (19.9%), respiratory, thoracic and mediastinal disorders (12.6%), and psychiatric disorders (12.6%). Immune system disorders included seasonal allergies (16.2%), drug hypersensitivity (4.3%), and various other allergies (≤1.1%). Respiratory, thoracic and mediastinal disorders included asthma (8.4%) and allergic rhinitis (2.9%). Attention deficit/hyperactivity disorder was the most frequently reported psychiatric disorder (9.6% of the FAS). Proportions of pre-existing conditions were similar between age cohorts except that fewer subjects 5-8 years (9.5%) than 9-17 years (15.7%) reported psychiatric disorders. A total of 6 subjects [all in the Afluria QIV group, (0.4%)] had type 1 or 2 diabetes mellitus or insulin resistance. No immunodeficiency disorders or other immunosuppressive conditions were reported at baseline. A total of 20 (0.9%) of

subjects reported obesity [weight but not height was measured, and body mass index (BMI) was not calculated in the study].

Concomitant Medications

A total of 40.8% of subjects in the FAS reported taking concomitant medications prior to vaccination or during the study period. Proportions were similar between treatment groups and age cohorts. Overall, the percentages of subjects who reported taking ibuprofen/naproxen or acetaminophen-containing medications were 8.9% and 6.6%, respectively.

Reviewer comment: Medication use, including antipyretics, was similar between treatment groups. Evaluation of the CSR and electronic datasets indicated that a total of 4 subjects, 2 in each treatment group, received low dose and/or short course (e.g., one day) oral glucocorticoids during the study for exacerbation of asthma, cough, croup, and mononucleosis. No significantly immunosuppressive agents were reported.

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-13-02*

Population*	**Afluria QIV N (%)****	**Comparator QIV N (%)****	**Total N (%)****
Screened, n	--	--	2349
Screening failures, n	--	--	71
Full Analysis Set (FAS), n(%)	1709 (100)	569 (100)	2278 (100)
Randomized, withdrew before vaccination, n	1	2	3
Vaccinated but provided no safety data, n	16	7	23
Overall Safety Population, n(%)	1692 (99.0)	560 (98.4)	2252 (98.9)
Solicited Safety Population, n(%)	1621 (94.9)	535 (94.0)	2156 (94.6)
Solicited Safety Population after 1st Vaccination	1618 (94.7)	532 (93.5)	2150 (94.4)
Solicited Safety Population after 2nd Vaccination	178 (10.4)	63 (11.1)	241 (10.6)
Evaluable Population, n(%)[1]	1622 (94.9)	533 (93.7)	2155 (94.6)
Per Protocol Population, n(%)[2]	1605 (93.9)	528 (92.8)	2133 (93.6)
Completed study, n(%)	1628 (95.3)	535 (94.0)	2163 (95.0)
Discontinued from study, n(%)	81 (4.7)	34 (6.0)	115 (5.0)
Adverse event, n	0	0	0
Death, n	0	0	0
Lost to follow-up, n(%)	67 (3.9)	25 (4.4)	92 (4.0)
Other, n[3]	2 (0.1)	1 (0.2)	3 (0.1)
Investigator decision, n	3 (0.2)	0	3 (0.1)
Withdrawal by subject, n	9 (0.5)	8 (1.4)	17 (0.7)

Source: Adapted from STN 125254/642, Module 5, CSLCT-QIV-13-02 CSR, Tables 14.1.1.1, Figures 10.1-1 and 10.1-2, and text pp.96-100.

*ClinicalTrials.gov identifier: NCT02545543

**Percentages based on number of subjects in Full Analysis Set (FAS) in each group.

[1]The Evaluable Population (EP) excluded 123 subjects in the FAS who: withdrew before vaccination (n=3); did not have valid pre- and post-vaccination serologies (n=114); received prohibited medications (n=6); and had a laboratory-confirmed influenza-like illness between Visit 1 and Exit Visit (n=0).

[2]The Per Protocol Population excluded 22 subjects in the EP (total n=145 excluded from FAS) with protocol deviations medically assessed as potentially impacting immunogenicity results: received influenza vaccine in last 6 months (n=2); fever or other signs of active infection within 48 hours prior to vaccination (n=10); incorrectly assigned to two dose regimen (n=3); Visit 2 >49 days after Visit 1 (first vaccination) (n=7); administered blinded pre-filled syringe #1505 instead of #1504, in error (n=1); and did not receive full dose because syringe cracked during vaccination (n=1).

[3]Other reasons for discontinuation from the study included non-compliance with study procedures (n=1) and parents trying to enroll subjects at more than one study site (n=2).

Reviewer comment: Evaluation of the electronic datasets confirmed the Applicant's report of subject disposition. Overall, 5.0% of subjects discontinued the study, most were lost to follow-up (4.0%), and none were due to AEs. The dropout/discontinuation rates were relatively low, similar across treatment groups, and should not have significantly impacted the interpretation of immunogenicity or safety results.

Subject disposition for the two age cohorts was similar to the overall study population except that relatively more subjects 5-8 years than 9-17 years discontinued the study (7.9% vs 2.1%), 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 – CSLCT-QIV-13-02 (Full Analysis Set)*

Age Group	**5-8 yrs**	**5-8 yrs**	**5-8 yrs**	**9-17 yrs**	**9-17 yrs**	**9-17 yrs**
Population, n(%)**	**Afluria QIV N(%)**	**Comparator QIV N(%)**	**Total N(%)**	**Afluria QIV N(%)**	**Comparator QIV N(%)**	**Total N(%)**
Full Analysis Set	875 (100)	291 (100)	1166 (100)	834 (100)	278 (100)	1112 (100)
Overall Safety Population	865 (98.9)	286 (98.3)	1151 (98.7)	827 (99.2)	274 (98.6)	1101 (99.0)
Solicited Safety Population	829 (94.7)	274 (94.2)	1103 (94.6)	792 (95.0)	261 (93.9)	1053 (94.7)
Solicited Safety 1	826 (94.4)	271 (93.1)	1097 (94.1)	792 (95.0)	261 (93.9)	1053 (94.7)
Solicited Safety 2	178 (20.3)	63 (21.6)	241 (20.7)	n/a	n/a	n/a
Evaluable Population	810 (92.6)	265 (91.1)	1075 (92.2)	812 (97.4)	268 (96.4)	1080 (97.1)
Per Protocol Population	795 (90.9)	262 (90.0)	1057 (90.7)	810 (97.1)	266 (95.7)	1076 (96.8)
Completed Study	810 (92.6)	264 (90.7)	1074 (92.1)	818 (98.1)	271 (97.5)	1089 (97.9)
Discontinued Study	65 (7.4)	27 (9.3)	92 (7.9)	16 (1.9)	7 (2.5)	23 (2.1)
Adverse event	0	0	0	0	0	0
Lost to follow-up	56 (6.4)	21 (7.2)	77 (6.6)	11 (1.3)	4 (1.4)	15 (1.3)
Other	2 (0.2)	1 (0.3)	3 (0.3)	0	0	0
Investigator decision	2 (0.2)	0	2 (0.2)	1 (0.1)	0	1 (<0.1)
Withdrawal by subject	5 (0.6)	5 (1.7)	10 (0.9)	4 (0.5)	3 (1.1)	7 (0.6)

Source: STN 125254/642, Module 5, CSLCT-QIV-13-02 CSR, Tables 14.1.1.2 and 14.1.1.3
*ClinicalTrials.gov identifier: NCT02545543
**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
n/a = not applicable

Reviewer comment: As specified by the protocol, at least 50% (51.2% or 1166 of 2278 in the FAS) of all subjects were randomized to the 5-8 year age stratum.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoints

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. Non-inferiority of Afluria QIV compared to Comparator QIV was assessed for the co-primary endpoints of HI GMT ratios and SCR differences for each of the four virus strains as described in Section 6.1.8, Endpoints and Criteria for Success.

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 5 through 17 years.

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 5 through 17 Years (Per Protocol Population) – CSLCT-QIV-13-02*

Strain	GMT[1] Afluria QIV (n=1605)[6]	GMT[1] Comparator QIV (n=528)	GMT[1,2] Ratio (95% CI)	SCR[3] Afluria QIV (n=1605) (95% CI)	SCR[3] Comparator QIV (n=528) (95% CI)	SCR[4] Difference (95% CI)	Met NI Criteria?[5]
A/H1N1	952.6	958.8	1.01 (0.93, 1.09)	66.4 (64.0, 68.7)	63.3 (59.0, 67.4)	-3.1 (-8.0, 1.8)	Yes
A/H3N2	886.4	930.6	1.05 (0.96, 1.15)	82.9 (81.0, 84.7)	83.3 (79.9, 86.4)	0.4 (-4.5, 5.3)	Yes
B/Yamagata	60.9	54.3	0.89 (0.81, 0.98)	58.5 (56.0, 60.9)	55.1 (50.8, 59.4)	-3.4 (-8.3, 1.5)	Yes
B/Victoria	145.0	133.4	0.92 (0.83, 1.02)	72.1 (69.8, 74.3)	70.1 (66.0, 74.0)	-2.0 (-6.9, 2.9)	Yes

Source: STN 125254/642, Module 5, CSLCT-QIV-13-02 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/Switzerland/9715293/2013 (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.
*ClinicalTrials.gov identifier: NCT02545543
[1]GMTs adjusted for covariates: treatment group, age subgroup, sex, vaccination history, pre-vaccination GMT, 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 8400394-0046 was excluded from the PPP for the adjusted GMT analysis for the GMT ratio because the subject did not have information on all covariates (i.e., unknown previous vaccination history)

Reviewer comment: Afluria QIV met the eight pre-specified co-primary endpoints required to demonstrate NI to Comparator QIV vaccines in children and adolescents 5 through 17 years. GMTs and GMT ratios calculated from unadjusted GMTs were very similar to GMTs and GMT ratios adjusted for covariates (see CSLCT-QIV-13-02 CSR Table 14.2.1.1) and also met NI criteria.

Reviewer comment: As specified in the SAP, the primary NI analyses were also conducted on the EP because there was a >1% variation between the PPP and the EP in the 5-8 year age group (1.67%). Results of the primary NI analyses based on the EP were very similar to those based on the PPP (see CSLCT-QIV-13-02 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. The 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.

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. 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 Sect 6.1.11.1), and are summarized only briefly in this section. Detailed results of these analyses are found in Tables 11.4-2, 11.4-3, 14.2.4.1, 14.2.4.2, 14.2.5.1, 14.2.5.2, 14.2.6.1, and 14.2.6.2 of the CSR for CSLCT-QIV-13-02 (STN 125254/642 Module 5).

- Pre-vaccination (Day 1) GMTs for each of the four vaccine virus strains were similar across treatment groups within each age cohort and between age cohorts. Across age and treatment groups, pre-vaccination GMTs to the B virus strains (point estimates ranging 9.4-19.2) were statistically significantly lower as compared to the A strains (point estimates ranging 65.0-124.0). Post-vaccination (28 days after the final dose) unadjusted GMTs were generally similar across age and treatment groups, with statistically significantly lower titers elicited against the B strains, particularly for B/Yamagata. Point estimates for post-vaccination GMTs for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria in Afluria recipients 5-8 years were 762.6, 911.8, 51.9, and 135.3, respectively. Point estimates for post-vaccination GMTs for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria in Afluria recipients 9-17 years were 964.8, 709.8, 70.8, and 146.6, respectively.
- For A/H1N1 and A/H3N2, pre-vaccination percentages of subjects with HI titers of ≥1:40 (% HI ≥1:40) were similar between age and treatment groups whereas pre-vaccination % HI ≥1:40 for both B strains were slightly higher in the 9-17 years group relative to the 5-8 years group. Post-vaccination % HI ≥1:40 were similar between age and treatment groups but were statistically significantly higher for the A strains as compared to B strains, and statistically significantly higher for B/Victoria as compared to B/Yamagata. 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 5-8 years were 98.9%, 98.4%, 65.8%, and 86.0%, respectively. The LBs on the two-sided 95% CI for the % HI ≥1:40 in children and adolescents 9-17 years who received Afluria QIV were 99.1%, 98.9%, 77.7%, and 90.0%, respectively. The LBs on the two-sided 95% CI for the % HI ≥1:40 in children and adolescents 5-17 years who received Afluria QIV were 99.3%, 98.9%, 72.8% and 88.7%, respectively.
- Seroconversion rates to the study vaccine strains were similar between treatment and age groups, and were 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 64.6%, 80.5%, 52.2%, and 70.4%, respectively, in children 5-8 years; 61.4%, 79.8%, 57.8%, and 67.3%, respectively, in children and adolescents 9-17 years; and 64.0%, 81.0%, 56.0%, and 69.8%, in children and adolescents 5-17 years.

Reviewer comment: Except for the B/Yamagata strain in children 5-8 years, 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%, for each of the four vaccine antigens, in subjects 5 through 17 years, overall and within each age cohort. Children 5-8 years just missed the % HI ≥1:40 endpoint for B/Yamagata in both treatment

groups: LBs of the 95% CI for % HI ≥1:40 for Afluria QIV and Comparator QIV in the younger age cohort were 65.8% and 63.1%, respectively.

Reviewer comment: Lower pre- and post-vaccination HI GMTs 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, especially in the younger age cohort. According to DVP, use of whole rather than split virus in the HI assay for the B strains (but not for the A strains) may also have contributed to low HI titers for the B strains, but less previous exposure remains the primary explanation for lower immune responses to the B antigens relative to the A antigens. 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 post-hoc descriptive analyses not powered to demonstrate differences between sub-groups.

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-13-02**

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=827**	**Female N=778**	**Male N=827**	**Female N=778**	**Male N=827**	**Female N=778**
A/H1N1	831.3 (780,886)	888.9 (836,945)	98.6%	99.5%	62.2%	63.8%
A/H3N2	808.4 (752,869)	798.5 (741,860)	98.6%	98.7%	81.6%	78.6%
B/Yamagata	61.1 (57,66)	60.2 (56,65)	71.9%	71.7%	56.2%	53.8%
B/Victoria	141.1 (130,153)	140.6 (129,153)	87.8%	88.2%	70.0%	67.6%

Source: STN 125254/642, Module 5, CSLCT-QIV-13-02 CSR, Tables 14.2.4.3 and 14.2.6.3
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=827 (51.5%); Female, n=778 (48.5%)
**ClinicalTrials.gov identifier: NCT02545543

Differences in immune responses between male and female recipients of Afluria QIV were not statistically significant. At CBER's request, the Applicant provided additional subanalyses of non-inferiority according to sex (STN 125254.642.3, data not shown). GMT ratios between males and females were not statistically significantly different, and, in both subgroups, UBs of the 95% CI were <1.5 for each vaccine strain. SCR differences between males and females were not statistically significantly different, and, in both subgroups, UBs of the 95% CI were <10% for each vaccine strain.

Reviewer comment: Differences in immune responses between male and female recipients of Afluria QIV were not statistically significant. Subanalyses suggested trends towards non-inferior GMT ratios and SCR differences for Afluria QIV relative to Comparator QIV in both males and females.

Race

The majority of subjects in the PPP were white (n=1584, 74.3%). Black/African American subjects comprised 19.9% (n=424) 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-13-02**

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=1180**	**Black N=324**	**White N=1180**	**Black N=324**	**White N=1180**	**Black N=324**
A/H1N1	812.9 (770,858)	1064.0 (979,1156)	99.0%	98.9%	62.7%	65.7%
A/H3N2	768.7 (722,818)	968.5 (875,1073)	98.9%	97.8%	81.8%	75.5%
B/Yamagata	59.1 (55,63)	68.1 (61,76)	70.8%	75.8%	55.0%	56.5%
B/Victoria	137.5 (128,147)	161.6 (142,184)	88.1%	87.8%	69.2%	67.6%

Source: STN 125254/642, Module 5, CSLCT-QIV-13-02 CSR, Tables 14.2.4.4, 14.2.6.4
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=1180 (73.5%); Black, n=324 (20.2%)
**ClinicalTrials.gov identifier: NCT02545543

Post-vaccination (28 days after the last vaccination) GMTs in blacks or African American recipients of Afluria QIV were statistically significantly higher (non-overlapping 95% CIs) as compared to whites for the A/H1N1 and A/H3N2 strains included in the vaccines. However, post-vaccination % HI ≥1:40 and SCRs were generally similar between the two racial subgroups. At CBER's request, the Applicant also conducted descriptive sub-population analyses of GMT ratios and SCR differences for Afluria QIV relative to Comparator QIV (STN 125254/642.3, data not shown). GMT ratios of Afluria QIV as compared to Comparator QIV for blacks and white subgroups were similar, not statistically significantly different (overlapping 95% CIs), and were <1.5 for all vaccine strains. SCR differences between blacks and whites were not statistically significantly different (overlapping 95% CIs) and were <10% for all four strains in both racial subgroups, suggesting a trend towards non-inferior GMT ratios and SCR differences in both blacks and whites.

Ethnicity

The majority of all subjects in the PPP were non-Hispanic/Latino (n=1627, 76.3%). Hispanic/Latino subjects comprised 23.5% (n=501) of the PPP. Descriptive sub-analyses of GMTs, post-vaccination % HI ≥1:40, and SCRs were conducted for Hispanic/Latino and non-Hispanic/Latino ethnicity. 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-13-02**

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=1215**	**Hispanic/ Latino N=386**	**Non-Hispanic/ Latino N=1215**	**Hispanic/ Latino N=386**	**Non-Hispanic/ Latino N=1215**	**Hispanic/ Latino N=386**
A/H1N1	866.3 (824,911)	840.8 (766,923)	99.3%	98.1%	65.3%	56.1%
A/H3N2	843.0 (796,893)	697.2 (621,782)	99.2%	97.0%	82.7%	72.4%
B/Yamagata	61.1 (57,65)	59.8 (54,67)	72.7%	69.4	55.9%	52.9%
B/Victoria	139.7 (131,149)	146.4 (130,165)	88.4%	87.6%	70.5%	64.3%

Source: STN 125254/642, Module 5, CSLCT-QIV-13-02 CSR, Tables 14.2.4.5, 14.2.6.5
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=1215 (75.7%); Hispanic/Latino, n=386 (24.0%)
**ClinicalTrials.gov identifier: NCT02545543

Post-vaccination (28 days after the final vaccination) GMTs and post-vaccination % HI ≥1:40 in Hispanic/Latino recipients of Afluria QIV were similar to non-Hispanic/Latinos for the four vaccine strains included in the vaccines except for the A/H3N2 strain which elicited statistically significantly lower GMTs in Hispanic/Latinos than in non-Hispanic/Latinos (non-overlapping 95% CIs). SCRs were lower in Hispanic/Latino recipients than in non-Hispanic/Latino recipients of Afluria QIV for all four vaccine strains, but the differences were not statistically significant (95% CIs were overlapping). GMT ratios and SCR differences between Hispanic/Latinos and non-Hispanic/Latinos were not statistically significant (overlapping 95% CIs, data not shown). Hispanic/Latinos did not meet NI criteria for the SCR difference for the A/H3N2 strain (UB 95% CI 14.3). However, the small sample size contributed to wide 95% CIs and the descriptive nature of the analysis does not allow firm conclusions.

Reviewer comment: Overall, subanalyses of immune responses by sex, race, and ethnicity followed the patterns observed in the overall Per Protocol Population, and were generally similar between treatment groups. Descriptive subgroup analyses showed a trend towards statistically significant (non-overlapping 95% CIs) higher post-vaccination GMTs in black as compared to white recipients of Afluria QIV, and non-statistically significant (overlapping 95% CIs) lower SCRs in Hispanic/Latinos as compared to non-Hispanic/Latinos. The clinical significance of these observations is not clear 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.

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 not imputed. Overall, 5.0% of subjects discontinued the study, mostly lost to follow-up (4.0%). The discontinuation rate was similar between treatment groups and was not likely to introduce bias or impact interpretation of immunogenicity results.

6.1.11.5 Exploratory and Post Hoc Analyses

Exploratory Analyses (Immunogenicity)

Covariate analyses of HI GMTs and SCRs were conducted to evaluate the effect of baseline characteristics on the immune response. These analyses suggested that both pre-vaccination HI titer and receipt of influenza vaccine in the 12 months prior to study vaccination influenced GMTs and SCRs for all four strains. Subjects with high pre-vaccination HI GMT titers were more likely to have high post-vaccination GMTs but less likely to achieve seroconversion (a 4-fold rise in titer). Subjects who were vaccinated in the previous 12 months had lower GMTs and SCRs than those who had not been vaccinated in the previous 12 months. Subjects with any prior influenza vaccination history had lower GMTs to all four strains and lower SCRs to A/H1N1, A/H3N2, and B/Yamagata as compared to subjects without any prior influenza vaccination history. There were no clear associations between sex, age stratum, or number of doses and immune responses.

Reviewer comment: The positive effect of pre-vaccination GMTs on post-vaccination titers and inverse effect on SCRs are consistent with observations reported in other studies of influenza vaccines. The impact of vaccination in previous seasons is not well-understood and is an area of active research.

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 58 (2.5%) of subjects in the FAS [45 of1709 (2.6%) Afluria QIV recipients and 13 of 569 (2.3%) Comparator QIV recipients] reported having an ILI. One subject (Afluria QIV #8400289-0087) had laboratory-confirmed influenza infection. This case is discussed in Section 6.1.12.4, Non-fatal SAEs.

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 2,252 subjects, including 1692 and 560 who were vaccinated with Afluria QIV and Comparator QIV, respectively. Data was 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 focused on the SSP (Solicited AEs following any vaccination), and are presented according to age stratum due to 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 14 summarizes all solicited and unsolicited AEs reported in CSLCT-QIV-13-02 according to treatment group and overall.

Reviewer comment: All solicited local AEs were considered related to the study vaccines and are termed adverse reactions. 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 quite similar to placebo recipients. Solicited systemic AEs in this study were assessed for relatedness and 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-13-02**

Parameter	Afluria QIV N=1692 (%)*	Comparator QIV N=560 (%)*	Overall N=2252 (%)*
One or more Adverse Events (AE)	64.4	59.8	63.3
Maximum Intensity[1]			
• Grade 1	37.6	34.5	36.8
• Grade 2	20.8	20.0	20.6
• Grade 3	6.0	5.4	5.8
One or more related AEs	59.2	55.2	58.2
Discontinuations due to AE	0	0	0
Solicited Adverse Events – Any[2]	62.9	59.6	62.1
Maximum Intensity[1]			
• Grade 1	38.7	37.4	38.4
• Grade 2	18.4	17.6	18.2
• Grade 3	5.7	4.7	5.4
• Missing	<0.1	0	<0.1
Solicited Local Adverse Reactions[2,3]	56.1	52.1	55.1
• Cellulitis-like reaction	<0.1	0	<0.1
Solicited Systemic Adverse Events[2]	30.8	27.5	30.0
• Related solicited systemic AEs[4]	24.2	22.4	23.7
Unsolicited Adverse Events – Any	14.4	12.0	13.8
Maximum Intensity[1]			
• Grade 1	8.0	5.4	7.4
• Grade 2	5.8	5.7	5.8
• Grade 3	0.5	0.9	0.6
• Missing	<0.1	0	<0.1
Related Unsolicited AEs[4]	3.8	1.8	3.3
Serious Adverse Events (SAE)	0.5	0.4	0.4
Related SAEs[4]	0	0	0
Discontinuation due to SAE	0	0	0
Deaths	0	0	0
Adverse Events of Special Interest	0	0	0

Source: Adapted from STN 125254/642, Module 5, CSLCT-QIV-13-02 CSR Tables 12.2.1-1, 14.3.1.1.1, 14.3.1.1.6, 14.3.1.3.8, 14.3.1.6, 13.4.1.7.1, 14.3.1.8.1. STN 125254/642.5, Module 5, CSLCT-QIV-13-02 CSR Tables 12.2.1-1, 14.3.1.1.1.1, 14.3.1.1.6.1, 14.3.1.7.1.1, 14.3.1.8.1.1, 14.3.1.9.1.1, 14.3.1.9.4.1
Abbreviations: QIV=quadrivalent influenza vaccine
*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: NCT02545543
[1]Subjects were counted only once for multiple events of the same intensity
[2]Solicited Safety Population: Afluria QIV=1621; Comparator QIV=535; Overall=2156
[3]All solicited local adverse reactions were considered related to study vaccine.
[4]Relatedness as assessed by the Investigator. One SAE (of influenza) was assessed as related by the Applicant but not by the Investigator.

Reviewer comment: Recipients of Afluria QIV reported slightly more AEs overall as compared to recipients of Comparator QIV, 64.4% vs 59.8%, respectively, both for solicited AEs (62.9% vs 59.6%, respectively) and unsolicited AEs (14.4% vs 12.0%, respectively). However, the imbalances were small.

Solicited Adverse Events

Solicited Local AEs – Subjects 5 through 8 Years

Table 15 summarizes the rates of solicited local AEs reported in the seven days following vaccination (Day 1 through Day 7) in subjects 5-8 years according to dose, treatment, and maximum severity.

Table 15: Solicited Local Adverse Reactions by Dose and Maximum Severity, Subjects 5 through 8 Years (Solicited Safety Population)* – CSLCT-QIV-13-02**

--	Local AE	Afluria N=829	Afluria N=829	Afluria N=829	Afluria N=829	Comp N=274	Comp N=274	Comp N=274	Comp N=274	Overall N=1103
Dose	Reaction	Mild %[1]	Mod %[1]	Sev %[1]	All %[1]	Mild %[1]	Mod %[1]	Sev %[1]	All %[1]	All %[1]
Any	Any	39.2	12.4	5.5	57.2	41.0	8.8	4.0	54.0	56.4
Any	Pain	42.1	8.3	0.8	51.3	42.1	6.6	0.7	49.6	50.8
Any	Redness	10.9	5.1	3.5	19.4	14.2	2.6	1.8	18.6	19.2
Any	Swelling	4.9	7.0	3.4	15.3	6.2	4.0	2.2	12.4	14.6
1st	Any	38.7	11.1	5.2	55.1	40.0	9.3	3.7	53.1	54.6
1st	Pain	40.9	7.3	0.8	49.0	41.9	6.3	0.7	49.1	49.0
1st	Redness	11.4	4.5	3.3	19.1	14.0	2.6	1.5	18.1	18.9
1st	Swelling	4.7	6.3	3.0	14.0	6.3	4.1	2.2	12.5	13.7
2nd	Any	24.7	10.1	2.2	37.1	31.7	1.6	1.6	34.9	36.5
2nd	Pain	28.1	6.7	0	34.8	28.6	1.6	0	30.2	33.6
2nd	Redness	3.9	4.5	1.1	9.6	7.9	0	1.6	9.5	9.5
2nd	Swelling	3.9	5.1	2.2	11.2	4.8	0	0	4.8	9.5

Source: STN 125254.642, Module 5, CSLCT-QIV-13-02 CSR, Tables 12.2.2-1, 14.3.1.2.2, 14.3.1.2.3, and 14.3.1.2.4

*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 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: NCT02545543

[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 and pain: Afluria QIV n=829; Comparator QIV n=273; Overall n=1102; and for swelling and redness: Afluria QIV n=829, Comparator QIV n=274, Overall n=1103. For SSP-1 after Dose 1, # of subjects with non-missing data for any AE and pain: Afluria QIV n=826, Comparator QIV n=270, Overall n=1096; and for redness and swelling: Afluria QIV n=826, Comparator QIV n=271, Overall n=1097. For SSP-2 after Dose 2, # of subjects with non-missing data for any AE, pain, swelling and redness: Afluria QIV n=178, Comparator n=63, Overall n=241.

A total of 1103 subjects 5 through 8 years (829 and 274 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, 57.2% and 54.0% of Afluria QIV and Comparator QIV recipients reported any local reaction, primarily pain (51.3% and 49.6%, respectively), followed by redness (19.4% and 18.6%) and swelling (15.3% and 12.4%, respectively). Most reactions were mild to moderate in severity. The rates of any severe local reaction were 5.5% and 4.0% for Afluria QIV and Comparator QIV, respectively. Although rates of local reactions were generally similar between treatment groups, there was a small imbalance in the overall rate of local swelling between Afluria QIV and Comparator QIV recipients (as noted) and in the rates

of severe local swelling (3.4% vs 2.2%, respectively) and severe redness (3.5% vs 1.8%, respectively), with Afluria QIV recipients reporting more severe reactogenicity. The mean onset of all local reactions in the 5-8 years 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 1097 subjects 5-8 years (826 Afluria QIV and 271 Comparator QIV recipients, respectively) provided solicited safety data following the first vaccination while 241 subjects (178 Afluria QIV and 63 Comparator QIV recipients, respectively) provided solicited safety data following the second vaccination. Pain was the most frequently reported local reaction following both the first and second vaccinations, (overall rates 49.0% and 33.6%, respectively), followed by redness (overall 18.9% and 9.5%, respectively) and swelling (overall 13.7% and 9.5%). Rates of all three local reactions declined following the second vaccination and, for pain and redness, were similar between treatment groups and mostly mild to moderate in severity. The overall rates of local swelling declined to a lesser extent following the second vaccination with Afluria QIV (Dose 1 = 14.0%, Dose 2 = 11.2%) as compared to Comparator QIV (Dose 1 = 12.5%, Dose 2 = 4.8%). The rates of severe local swelling and redness declined following the second vaccination in both treatment groups (no subjects reported severe pain after the second vaccination), with small imbalances between recipients of Afluria QIV and Comparator QIV (severe swelling after Dose 2 = 2.2% vs 0, respectively; severe redness after Dose 2 = 1.1% vs 1.6%, respectively).

Cellulitis-like reaction
One subject who received Afluria QIV had a cellulitis-like reaction. A case narrative was requested and the electronic datasets reviewed for Subject #8400399-0066, an 8-year old white female, who had concurrent severe (Grade 3) pain, swelling (up to 78 mm), and redness (up to 78 mm) from Day 3 to Day 7 after the first vaccination. The subject was previously vaccinated for influenza in December 2014. She received Afluria QIV on October 10, 2015 (Day 1) and reported Grade 2 injection site pain on Days 1 and 2. On Day 2, she had severe injection site redness and swelling (both 50 mm), and on Day 3 (October 12, 2015), concurrent Grade 3 pain, redness, and swelling. Diphenhydramine and topical hydrocortisone were administered to treat the reaction which resolved by Day 11 (October 20, 2015). The subject had no fever but had Grade 2 solicited systemic AEs of diarrhea, headache, malaise, and fatigue from Day 1 to Day 4. The investigator assessed all the events as related to study vaccine.

Reviewer comment: Small imbalances in the rates of severe injection site redness and swelling, including one case of a cellulitis-like reaction, between treatment groups did not appear to be clinically significant given the relatively low rates of these events and the Applicant's report that no subjects were discontinued from the study due to AEs. More local reactogenicity was also observed among adult recipients of Afluria QIV ≥18 years relative to a U.S.-licensed comparator in study CSLCT-QIV-13-01 (please see the clinical review of STN 125254/565). The Applicant had also reported an increase in postmarketing reports of large injection site swelling and cellulitis in 2011, and added these events to Section 6.2 (Postmarketing Experience) of the Package Insert. Postmarketing reports are monitored by Seqirus, and, according to subsequent annual Drug Safety Update Reports (DSUR) for Afluria (trivalent formulation, IND 12997), rates appear to have since declined and stabilized. Please see the OBE/DE review for additional discussion of postmarketing reports.

Solicited Local AEs – Subjects 9 through 17 Years

Table 16 summarizes the rates of solicited local AEs reported in the seven days following vaccination (Day 1 through Day 7) in subjects 9-17 years according to treatment and maximum severity.

Table 16: Solicited Local Adverse Reactions by Maximum Severity, Subjects 9 through 17 Years (Solicited Safety Population) – CSLCT-QIV-13-02*

Local AE	Afluria N=792	Afluria N=792	Afluria N=792	Afluria N=792	Comp N=261	Comp N=261	Comp N=261	Comp N=261	Overall N=1053
Reaction	Mild %[1]	Mod %[1]	Sev %[1]	All %[1]	Mild %[1]	Mod %[1]	Sev %[1]	All %[1]	All %[1]
Any	37.5	14.2	3.2	54.9	34.1	12.3	3.8	50.2	53.8
Pain	40.5	10.6	0.3	51.5	36.0	8.8	0.4	45.2	50.0
Redness	8.8	4.0	1.9	14.8	10.3	3.8	1.9	16.1	15.1
Swelling	5.2	5.1	2.0	12.2	3.8	5.0	1.9	10.7	11.9

Source: STN 125254.642, Module 5, CSLCT-QIV-13-02 CSR, Tables 12.2.2-2 and 14.3.1.2.2
Abbreviations: 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=subjects with any local reaction.
*ClinicalTrials.gov identifier: NCT02545543
[1]Denominators for percentages based on # of subjects with non-missing data for each group and each parameter in the Solicited Safety Population (SSP): The # of subjects with non-missing data for any AE, swelling and redness: Afluria QIV n=792; Comparator QIV n=261; Overall n=1053; and for pain : Afluria QIV n=790, Comparator QIV n=261, Overall n=1053.

Among 1053 subjects 9 through 17 years (792 and 261 recipients of Afluria QIV and Comparator QIV, respectively) who provided safety data regarding solicited AEs following a single dose of study vaccine (Solicited Safety Population), 54.9% and 50.2%, respectively, reported any local reaction. Pain was most frequently reported (51.5% vs 45.2%, respectively), followed by redness (14.8% vs 16.1%, respectively) and swelling (12.2% vs 10.7%, respectively). Most reactions were mild in severity. Other than a slightly higher rate of pain in Afluria QIV recipients, rates and severity of local reactions were similar between treatment groups. The rates of any severe reaction in Afluria QIV and Comparator QIV recipients were 3.2% and 3.8%, respectively, comprised primarily of redness and swelling (ranging 1.9%-2.0% for both treatment groups). The mean onset of all local reactions in the 9-17 year age group occurred between Day 1 and Day 2. The mean durations of all local reactions ranged from 1.5 to 2 days and were similar between treatment groups.

In comparison to subjects 5-8 years, subjects 9-17 years in both treatment groups had slightly lower rates of local injection site reactions overall. Rates of severe local reactions following Afluria QIV were slightly higher in children 5-8 years as compared to the older age group while rates of severe local reactions following Comparator QIV were similar between age groups.

Reviewer comment: Rates of local injection site reactions in subjects 9 through 17 years were similar between treatment groups and did not suggest significant safety concerns. The slightly higher rates of local reactions in younger subjects, including higher rates of severe reactions among recipients of Afluria QIV, in this study appear acceptable. We will have a better understanding of the clinical significance of this small imbalance only after Afluria QIV is marketed to a broader patient population. The observed trend may also predict higher rates of local reactions in children <5 years, currently being studied in CSLCT-QIV-15-03.

Solicited Systemic Adverse Events – Subjects 5 through 8 Years

Table 17 summarizes the rates of solicited systemic AEs reported in the seven days following vaccination (Day 1 through Day 7) in subjects 5-8 years according to dose, treatment, and maximum severity.

Table 17: Solicited Systemic Adverse Events by Dose and Maximum Severity, Subjects 5 through 8 Years (Solicited Safety Population)* – CSLCT-QIV-13-02**

--	--	Afluria N=829	Afluria N=829	Afluria N=829	Afluria N=829	Comp N=274	Comp N=274	Comp N=274	Comp N=274	Overall N=1103
Dose	**Systemic AE**	**Mild %[1]**	**Mod %[1]**	**Sev %[1]**	**All %[1]**	**Mild %[1]**	**Mod %[1]**	**Sev %[1]**	**All %[1]**	**All %[1]**
Any	Any	17.9	8.1	1.6	27.6	15.0	9.9	1.5	26.3	27.3
Any	Headache	8.7	3.4	0.1	12.3	6.2	4.0	0.4	10.6	11.9
Any	Myalgia	7.2	2.4	0.1	9.8	8.8	2.2	0.4	11.3	10.2
Any	Malaise/ Fatigue	4.6	3.9	0.4	8.8	2.6	3.3	0	5.8	8.1
Any	Nausea	3.7	3.1	0.1	7.1	4.0	4.4	0	8.4	7.4
Any	Diarrhea	4.3	0.8	0	5.2	3.3	0.4	0	3.6	4.8
Any	Fever	1.9	1.3	1.2	4.5	1.5	1.5	0.7	3.6	4.3
Any	Vomiting	0.8	1.3	0.2	2.4	1.5	2.9	0	4.4	2.9
1st	Any	16.6	7.3	1.6	25.5	14.4	8.1	1.5	24.0	25.2
1st	Headache	7.9	3.2	0.1	11.3	5.5	3.7	0.4	9.6	10.8
1st	Myalgia	7.3	2.2	0.1	9.6	8.1	2.2	0.4	10.7	9.8
1st	Malaise/ Fatigue	4.0	3.8	0.4	8.1	2.6	3.0	0	5.5	7.5
1st	Nausea	3.8	2.8	0.1	6.8	3.7	3.7	0	7.4	6.9
1st	Diarrhea	3.6	0.8	0	4.5	3.0	0.4	0	3.3	4.2
1st	Fever	1.7	1.1	1.2	4.0	1.1	1.1	0.7	3.0	3.7
1st	Vomiting	0.8	1.1	0.2	2.2	1.5	1.5	0	3.0	2.4
2nd	Any	11.2	5.6	0	16.9	11.1	7.9	0	19.0	17.4
2nd	Headache	5.6	1.1	0	6.7	6.3	1.6	0	7.9	7.1
2nd	Myalgia	1.7	1.7	0	3.4	6.3	0	0	6.3	4.1
2nd	Malaise/ Fatigue	5.1	0.6	0	5.6	0	1.6	0	1.6	4.6
2nd	Nausea	1.7	1.7	0	3.4	1.6	3.2	0	4.8	3.7
2nd	Diarrhea	3.4	0.6	0	3.9	1.6	0	0	1.6	3.3
2nd	Fever	1.1	1.1	0	2.2	1.6	1.6	0	3.2	2.5
2nd	Vomiting	1.1	1.1	0	2.2	0	6.3	0	6.3	3.3

Source: STN 125254.642, Module 5, CSLCT-QIV-13-02 CSR, Tables 12.2.2-3, 14.3.1.3.2, 14.3.1.3.3, and 14.3.1.3.4

*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: NCT02545543

[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 and headache: Afluria QIV n=828, Comparator QIV n=274, Overall n=1102; for fever, vomiting, diarrhea, myalgia, and malaise/fatigue: Afluria QIV n=829, Comparator QIV n=274, Overall n=1103; for nausea: Afluria QIV n=828, Comparator QIV n=274, Overall n=1102. For the SSP-1, # of subjects with non-missing data for any AE, nausea, and headache: Afluria QIV n=825, Comparator QIV n=271, Overall n=1096; for fever, vomiting, diarrhea, myalgia, and malaise/fatigue: Afluria QIV n=826, Comparator QIV n=271, Overall n=1097. For theSSP-2, # of subjects with non-missing data for any AE, fever, nausea, vomiting, diarrhea, headache, myalgia, and malaise/fatigue: Afluria QIV n=178, Comparator n=63, Overall n=241.

Among 1103 subjects 5 through 8 years who provided safety data regarding solicited

AEs following any (first and/or second) vaccination, 27.6% and 26.3% of Afluria QIV and Comparator QIV recipients, respectively, reported solicited systemic AEs. The most frequently reported symptoms in both groups were headache (12.3% vs 10.6%), myalgia (9.8% vs 11.3%), malaise/fatigue (8.8% vs 5.8%), nausea (7.1% vs 8.4%), and diarrhea (5.2% vs 3.6%). Rates were similar between treatment groups with small imbalances observed for malaise/fatigue (as noted) and vomiting (Afluria QIV 2.4%, Comparator QIV 4.4%). Fever was uncommon, but rates of any fever among Afluria QIV recipients were slightly higher than Comparator QIV recipients (4.5% vs 3.6%, respectively) as were rates of severe Grade 3 fever (≥102.2°F or ≥39.0°C) (1.2% vs 0.7%). No fevers were associated with seizures. Most events were mild to moderate in severity with a total of 1.6% and 1.5% 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 4, with a mean duration of less than two days. The mean onset of fever was Day 3.1 for Afluria QIV and Day 3.5 for Comparator QIV, with similar durations of 1.2 to 1.3 days.

Rates of solicited systemic AEs following the first vaccination were similar to rates following any vaccination, occurring in 25.5% and 24.0% of Afluria QIV and Comparator QIV recipients, respectively. Rates of solicited systemic AEs following the second vaccination were lower than the first vaccination in both treatment groups, occurring in 16.9% of Afluria QIV and 19.0% of Comparator QIV recipients. The most common events following the second vaccination with Afluria QIV and Comparator QIV, respectively, were headache (6.7% vs 7.9%), malaise/fatigue (5.6% vs 1.6%), and myalgia (3.4% vs 6.3%). Fever occurred in 4.0% and 3.0% of Afluria QIV and Comparator QIV recipients, respectively, after the first vaccination and in 2.2% and 3.2%, respectively, after the second vaccination. Severe Grade 3 fever (≥102.2°F or ≥39.0°C) occurred in 1.2% and 0.7% of Afluria QIV and Comparator QIV recipients after the first vaccination, but was not reported by any subjects following the second vaccination. Most events following the first and second vaccination were mild to moderate in severity. A total of 1.6% and 1.5% of Afluria QIV and Comparator QIV recipients reported severe solicited systemic AEs following the first vaccination. No subjects reported severe solicited systemic AEs following 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 headache, malaise/fatigue, and diarrhea in recipients of Afluria QIV, and slightly higher rates of myalgia, nausea, and vomiting in recipients of Comparator QIV, no large imbalances or unusual patterns were observed. Rates of fever and severe fever after any vaccination were slightly higher among Afluria QIV recipients (4.5% and 1.2%, respectively) as compared to Comparator QIV (3.6% and 0.7%), but did not appear clinically significant, and are lower than historical rates [please see Section 2.4]. (b) (4) ***the four Afluria QIV vaccine virus strains used in this study may be associated with less pyrogenicity as suggested by Seqirus' scientific investigation. However, we do not know whether the lower rates of fever observed in CSLCT-QIV-13-02 are generalizable to a broader group of subjects 5-8 years, to other populations (i.e., younger children), or to future vaccine formulations containing different antigens. The occurrence of febrile reactions and febrile seizures will be monitored closely by OBE/DE through postmarketing surveillance.***

Solicited Systemic Adverse Events – Subjects 9 through 17 Years

Table 18 summarizes the rates of solicited systemic AEs reported in the seven days following vaccination (Day 1 through Day 7) in subjects 9-17 years according to treatment and maximum severity.

Table 18: Solicited Systemic Adverse Events by Maximum Severity, Subjects 9 through 17 Years (Solicited Safety Population) – CSLCT-QIV-13-02*

--	Afluria N=792	Afluria N=792	Afluria N=792	Afluria N=792	Comp N=261	Comp N=261	Comp N=261	Comp N=261	Overall N=1053
Systemic AE	**Mild %[1]**	**Mod %[1]**	**Sev %[1]**	**All %[1]**	**Mild %[1]**	**Mod %[1]**	**Sev %[1]**	**All %[1]**	**All %[1]**
Any	20.2	12.5	1.4	34.1	17.2	10.7	0.8	28.7	32.8
Headache	12.0	6.4	0.4	18.8	8.8	5.4	0.4	14.6	17.8
Myalgia	11.6	4.8	0.3	16.7	7.7	3.1	0.4	11.1	15.3
Malaise/ Fatigue	5.3	4.3	0.4	10.0	5.4	2.3	0	7.7	9.4
Nausea	4.9	2.8	0	7.7	4.2	3.8	0	8.0	7.8
Diarrhea	4.4	1.0	0	5.4	2.7	1.5	0	4.2	5.1
Fever	1.1	0.5	0.5	2.1	0.4	0.4	0	0.8	1.8
Vomiting	1.3	0.5	0	1.8	0.8	1.5	0	2.3	1.9

Source: STN 125254.642, Module 5, CSLCT-QIV-13-02 CSR, Tables 12.2.2-4, 14.3.1.3.2
Abbreviations: 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 reaction=subjects with any solicited systemic event after any vaccination; AE=adverse event.
*ClinicalTrials.gov identifier: NCT02545543
[1]Denominators for percentages based on # of subjects with non-missing data for each population, each group, and each parameter. For the Solicited Safety Population (SSP), # of subjects with non-missing data for any AE, headache, nausea, vomiting, diarrhea, myalgia, malaise/fatigue, and fever: Afluria QIV n=792, Comparator QIV n=261, Overall n=1053.

Among 1053 subjects 9 through 17 years who received a single vaccination, 34.1% and 28.7% of Afluria QIV and Comparator QIV recipients, respectively, experienced solicited systemic AEs. Afluria QIV recipients had higher rates of certain events, i.e., headache, myalgia, malaise/fatigue and fever. The most common events reported by Afluria QIV and Comparator QIV recipients, respectively, were headache (18.8% vs 14.6%), myalgia (16.7% vs 11.1%), and malaise/fatigue (10.0% vs 7.7%). Fever occurred in 2.1% and 0.8% of Afluria QIV and Comparator QIV recipients, respectively, and were not associated with seizures. Overall, most solicited systemic AEs were mild to moderate in severity. A total of 1.4% and 0.8% of Afluria QIV and Comparator QIV, respectively, reported severe events. However, rates of severe AEs for all individual solicited systemic events were <1% in both treatment groups, including the rates of severe (Grade 3) fever (≥102.2°F or ≥39.0°C) which occurred in 0.5% of Afluria QIV but in none of the comparator group. Except for fever, the mean days of onset of solicited systemic AEs were similar between treatment groups. The mean onset of fever in Afluria QIV and Comparator QIV recipients was on Day 2.1 and Day 4.0, respectively, with a mean duration of 1.2 and 1.0 days, respectively.

Reviewer comment: Overall, Afluria QIV recipients experienced slightly more headache, myalgia, malaise/fatigue and fever following vaccination than the comparator group, and had more rapid onset of fever. Although this suggests that Afluria may be slightly more reactogenic than the comparator in a pediatric population 9-17 years, the rates of AEs did not appear unusual or clinically significant overall. Additionally, rates of severe AEs were low and similar between treatment groups.

Reviewer comment: 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.

Severe (Grade 3) Solicited Fever

The electronic datasets were evaluated further and case narratives requested for the twelve subjects [Afluria QIV = 10 (1.2%), Comparator QIV =2 (0.7%)] in the 5-8 year age stratum and four subjects [Afluria QIV = 4 (0.5%), Comparator QIV = 0)] in the 9-17 year age stratum who experienced severe (Grade 3) fever, defined as oral temperature ≥102.2°F or ≥39.0°C, following any vaccination. Many cases were accompanied by other constitutional symptoms of headache, sore throat, myalgia, malaise, and, occasionally, nausea, vomiting and/or diarrhea. Nine of the twelve Afluria recipients had onset of fever within 48 hours of vaccination, and all but two of the twelve events were assessed as related to study vaccine. One 6-year old Afluria QIV recipient appeared to have a concurrent otitis media and bronchitis. Most fevers were treated with acetaminophen and/or ibuprophen, and resolved within 24 hours. None of the cases were serious; all resolved without sequelae. Two Afluria QIV and one Comparator QIV recipient received a second vaccination without recurrent fever.

Reviewer comment: As previously noted, Afluria QIV recipients experienced slightly higher rates of any fever and severe fever as compared to Comparator QIV recipients. However, rates were lower than in previous trials of Afluria 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 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) ***the vaccine antigens can reduce the pyrogenicity of the vaccine in the pediatric population 5-17 years. Greater postmarketing exposure and surveillance will help confirm whether the study results are generalizable to a broader population 5-17 years. Results from the ongoing trial CSLCT-QIV-15-03 may help determine whether the modified formulation is associated with lower rates of fever in children 6-59 months.***

Subpopulation Analyses of Solicited Adverse Events

No very large clinically significant differences in the rates of solicited local injection site reactions or systemic symptoms were observed following vaccination with Afluria QIV or Comparatory QIV when analyzed by age stratum, sex, race, or ethnicity.

Age Stratum

Overall, subjects 5-8 years in both treatment groups experienced slightly higher rates of injection site redness and swelling and fever, but lower rates of certain solicited systemic symptoms as compared to the 9-17 age group (most notably headache). Please see Tables 15, 16, 17, and 18, and related text in the beginning of this section.

Sex

Overall, in the pediatric population 5-17 years, a total of 54.7% and 57.5% of male and female recipients of Afluria QIV, respectively, experienced solicited local injection site reactions. Differences in rates of specific reactions between males and females, respectively, were as follows: pain 49.0% vs 53.9%; redness 16.6% vs 17.8%; and swelling 12.8% vs 14.8%. Among the pediatric population 5-17 years, 29.9% 31.7% of male and female recipients of Afluria QIV experienced solicited systemic AEs.

Differences in rates of specific events between males and females, respectively, were as follows: fever 4.1% vs 2.5%; headache 14.6% vs 16.4%; myalgia 13.7% vs 12.6%; malaise/fatigue 9.0% vs 9.8%; nausea 7.6% vs 7.2%; diarrhea 5.2% vs 5.5; and vomiting 2.2% vs 2.0%.

Reviewer comment: Subpopulation analyses of solicited local reactions between male and female recipients of Afluria QIV showed a trend toward slightly higher rates of pain and swelling in females as compared to males. Males had more fever and females had more headache than the opposite sex.

Race
Among the pediatric population 5-17 years, 45.7% and 59.0% of black/African American and white recipients of Afluria QIV, respectively, experienced solicited local injection site reactions. Differences in rates of specific reactions between blacks/African Americans and whites, respectively, were as follows: pain 42.7% vs 53.7%; redness 7.3% vs 19.9%; and swelling 12.2% vs 14.0%. Among the pediatric population 5-17 years, 22.6% and 33.6% of black/African American and white recipients of Afluria QIV, respectively, experienced solicited systemic AEs. Differences in rates of specific events between blacks/African Americans and whites, respectively, were as follows: fever 3.4% vs 3.3%; headache 10.1% vs 17.1%; myalgia 10.1% vs 14.4%; malaise/fatigue 5.2% vs 10.8%; nausea 5.2% vs 8.2%; diarrhea 3.4% vs 5.9%; and vomiting 3.0% vs 2.0%.

Ethnicity
Among the pediatric population 5-17 years, 45.4% and 59.5% of Hispanic/Latino and non-Hispanic/Latino recipients of Afluria QIV, respectively, experienced solicited local reactions. Differences in rates of specific reactions between Hispanic/Latinos and non-Hispanic/Latinos, respectively, were as follows: pain 41.0% vs 54.7%; redness 9.8% vs 19.4%; and swelling 9.0% vs 15.4%. Among the pediatric population 5-17 years, 25.0% and 32.6% of Hispanic/Latino and non-Hispanic/Latino recipients of Afluria QIV, respectively, experienced solicited systemic AEs. Differences in rates of specific events between Hispanic/Latinos and non-Hispanic/Latinos, respectively, were as follows: fever 1.3% vs 4.0%; myalgia 10.8% vs %13.8; headache 10.1% vs 17.2%; malaise/fatigue 7.7% vs 9.9%; nausea 4.1% vs 8.5%; diarrhea 3.6% vs 5.9%; and vomiting 1.5% vs 2.3%.

Reviewer comment: Overall, subpopulation analyses showed trends towards more local injection site pain and swelling in females as compared to males, and more local and systemic reactogenicity in whites and non-Hispanic/Latinos as compared to blacks/African Americans and Hispanic/Latinos. Clinical trials of other influenza vaccines have shown a trend towards both more local and systemic reactogenicity in females as compared to males. However, the data do not allow firm conclusions because CSLCT-QIV-13-02 was not designed to analyze or detect statistically significant differences in rates of solicited local and systemic AEs between age strata or other subpopulations. 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 Fever
The Applicant explored the association between any fever and severe fever (potentially accompanied by any other solicited systemic AE) following administration of Afluria QIV

or Comparator QIV in the Overall Safety Population according to vaccine dose and baseline characteristics. Odds ratios with two-sided 95% CIs and p-values were calculated and revealed no significant associations between the occurrence of fever or severe fever with any variable, i.e., number of doses, age stratum, sex, previous influenza vaccination in 2014-15, or body weight.

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), v17.0.

Please see Table XX [at beginning of Sect 6.1.12.2] for an overview of unsolicited AEs, and CSLCT-QIV-13-02 CSR (STN 125254/642.5) Tables 12.2.2-5, 14.3.1.1.1, 14.3.1.1.2.1, 14.3.1.7.1.1, 14.3.1.7.2.1, 14.3.1.8.2.1, 14.3.1.9.1.1, 14.3.1.9.2.1, 14.3.1.9.3.1, 14.3.1.9.4.1, 14.3.1.9.5.1, and 14.3.1.9.6.1 for detailed summaries of unsolicited AEs by PTs and SOCs reported in each treatment group according to age cohorts 5-17 years, 5-8 years, and 9-17 years. A total of 310 subjects (13.8%) 5 through 17 years reported 503 spontaneous or unsolicited AEs in the 28 days following vaccination, with a slighter higher proportion of Afluria QIV recipients (14.4%) reporting unsolicited AEs as compared to Comparator QIV (12.0%). Among subjects 5 through 8 years, 16.2% and 15.0% of Afluria QIV (n=865) and Comparator QIV (n=286) recipients, respectively, reported one or more unsolicited AEs in the 28 days following any vaccination. Rates categorized by SOC were similar between treatment groups. A small imbalance was observed between treatment groups in the body system of General Disorders and Administration Site Conditions (Afluria QIV 4.3%; Comparator QIV 3.5%). The difference was driven by ILI (Afluria 0.9%, Comparator 0.3%) and small numbers of Afluria QIV recipients (≤0.3%) who had injection site events (e.g., warmth, bruising, erythema, induration, discoloration, or pain). Among subjects who received Afluria QIV, the most common unsolicited AEs (frequency ≥1%) were: cough (2.4%), pyrexia (1.8%), rhinorrhea (1.2%), and headache (1.0%). The most common AEs (frequency ≥1%) among Comparator QIV recipients were: cough (3.1%), pyrexia (2.8%), nasal congestion (1.7%), rhinorrhea (1.4%), oropharyngeal pain (1.4%), and vomiting (1.0%). Most AEs in both treatment groups were assessed as mild (58.8% of all events occurring in 8.4% of all subjects 5-8 years) or moderate (37.1% of all events occurring in 6.6% of all subjects 5-8 years) in severity, while 0.7% and 1.0% of Afluria QIV and Comparator QIV recipients, respectively, experienced severe AEs (3.7% and 4.2% of all AEs in the respective groups were severe). Only one subject (Afluria QIV recipient) was missing data regarding the severity of an AE. More Afluria QIV recipients than Comparator QIV (3.9% vs 2.4%, respectively) had unsolicited AEs assessed as related to study vaccine by the investigator.

Reviewer comment: Analyses of unsolicited AEs in children 5-8 years showed only small imbalances trending towards more influenza-like illness in Afluria QIV recipients and more cough, nasal congestion, oropharyngeal pain, and pyrexia 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 9 through 17 years, 12.5% of Afluria QIV (n=827) and 8.8%% of Comparator QIV (n=274) reported one or more unsolicited AEs in the 28 days following

vaccination. A small imbalance was observed between treatment groups in the body systems of Infections and Infestations (Afluria QIV 3.6%; Comparator QIV 1.5%) and General Disorders and Administration Site Conditions (Afluria QIV 1.9%; Comparator QIV 0.7%). The differences in these SOCs were driven by small numbers of Afluria QIV recipients (n=1-3, ≤0.2%) who had a variety of infections (respiratory, gastrointestinal, skin and soft tissue, viral and bacterial), constitutional symptoms (ILI, malaise, fatigue), and injection site events (bruising, discoloration, inflammation, pain). However, no large imbalances in individual types of AEs were observed. Among recipients of Afluria QIV 9 through 17 years, the most common unsolicited AEs (frequency ≥1%) were: oropharyngeal pain (1.6%), cough (1.3%), and upper respiratory tract infection (1.0%). Among Comparator QIV recipients, the most common unsolicited AEs (frequency ≥1%) were oropharyngeal pain (1.5%) and vomiting (1.1%). Most subjects in both treatment groups had AEs assessed as mild (56.8% of all events occurring in 6.3% of all subjects 9-17 years) or moderate (38.9% of all events occurring in 4.9% of all subjects 9-17 years) in severity, while 0.2% and 0.7% of Afluria QIV and Comparator QIV recipients, respectively, experienced severe AEs (2.6% and 11.1% of all AEs in the respective groups were severe). No subjects were missing data regarding the severity of AEs. As in the younger age cohort, more Afluria QIV recipients than Comparator QIV had AEs assessed as related to study vaccine by the investigator (3.6% vs 1.1%, respectively), although the overall rates were low and the difference between treatment groups relatively small.

Reviewer comment: More unsolicited AEs were reported by subjects 5-8 years as compared to 9-17 years, overall, 15.9% vs 11.5%, respectively, and by more recipients of Afluria QIV than Comparator QIV in both age strata (16.2% vs 15.0%, respectively, of subjects 5-8 years; 12.5% vs 8.8%, respectively, of subjects 9-17 years). However, the differences were relatively small, with no large imbalances or unusual patterns of specific events, and did not appear clinically significant. Evaluation of the electronic datasets yielded numbers of AEs identical to the Applicant's report.

Severity and Relatedness of Unsolicited Adverse Events

In the 28 days following any vaccination, a total of 8.0%, 5.8%, and 0.5% of recipients of Afluria QIV 5-17 years, reported unsolicited AEs of mild (Grade 1), moderate (Grade 2), or severe (Grade 3) intensity, respectively, as compared to 5.4%, 5.7%, and 0.9%, respectively, of Comparator QIV recipients. Overall, a total of 3.8% of Afluria QIV recipients were assessed by the investigator as having unsolicited AEs related to the study vaccine as compared to 1.8% of the comparator group. Six of the severe AEs were also assessed as serious and are discussed in Section 6.1.12.4.

In the 28 days following any vaccination, a total of 8 (0.5%) recipients of Afluria QIV experienced 13 severe unsolicited AEs. Of Afluria recipients 5-8 years, 6 (0.7%) had 9 severe events with 1 subject (0.1%) assessed as having a severe related AE ("local reaction to flu vaccine", preferred term of "vaccination site reaction"). Of Afluria recipients 9-17 years, 2 (0.2%) had 4 severe events with 1 subject (0.1%) assessed as having a severe related AE (sore throat). In comparison, a total of 5 (0.9%) Comparator QIV subjects experienced 7 severe AEs, including 3 (1.0%) subjects 5-8 years and 2 (0.7%) subjects 9-17 years. One (0.3%) Comparator QIV recipient 5-8 years had 1 severe AE (pyrexia) assessed as related. No Comparator QIV recipients 9-17 years had a severe related AE. With the exception of pyrexia, most of the severe unsolicited AEs were varied in type without unusual patterns or imbalances between treatment groups.

In the 28 days following any vaccination (excluding the solicited AE diary period), a total of three (0.2%) Afluria QIV and two (0.4%) Comparator QIV recipients reported unsolicited AEs of severe pyrexia (excludes pyrexia occurring during the solicited AE diary period and correctly recorded in the electronic diary). One AE of severe pyrexia (Comparator QIV subject ID #8400392-0013, 5-8 year age stratum) was considered related. Fever in this subject began on September 17, 2015, after receiving the second vaccination on that day, and lasted three days but was not recorded properly as a solicited AE (see reviewer comment below). AEs of severe pyrexia in the three Afluria QIV recipients began 7, 10, and 26 days post-vaccinations, and were assessed as not related.

Reviewer comment: Evaluation of the electronic datasets yielded severe unsolicited AE results consistent with the CSR text, tables (14.3.1.9.1, 14.3.1.9.4, 14.3.1.9.1.1, and 14.3.1.9.4.1) and listings (16.2.7.2). No unusual patterns were found. Among febrile events, only the case of fever (Subject #8400392-0013, 5-8 years) occurring on the same day as vaccination with Comparator QIV appeared related. Other fevers occurred 7 to 26 days post-vaccinations. The severe sore throat reported by Subject #8400393-0039 (Afluria QIV, 9-17 years) began three days post-vaccination, lasted 2 days, but appeared otherwise unremarkable. The severe vaccination site reaction reported by Subject #8400399-0066 (Afluria QIV, 5-8 years) was a continuation of a cellulitis-like reaction beyond the 7-day diary period (please see the review of this AE under Solicited Local AEs). The remaining severe unsolicited AEs appeared unrelated based on a lack of biological plausibility, alternative explanation, and/or lack of close temporal relationship.

Reviewer comment: Regarding the case of Grade 3 pyrexia that began on the day of the second vaccination in Subject #8400392-0013 (Comparator QIV), the Applicant explained (STN 125254/642.4, response to 12/16/16 IR) that this event was categorized as an unsolicited AE rather than a solicited AE because, despite receiving detailed instructions on completing the subject diary, the parents of the subject entered this AE not as a solicited AE but on the "Other Body Symptoms" page of the subject diary (used for ongoing solicited AEs Day 8 through 28 and unsolicited AEs). The parents did not record an actual temperature for this event and verbal recall during review of symptoms with study staff was not allowed. Of 29 subjects reported as having unsolicited AEs of pyrexia, Subject #8400392-0013 and two others (Subject #8400397-0072 and Subject #8400293-0023) had onset of fever during the 7-day post-vaccination solicited diary period. Subject #8400293-0023 was vaccinated with a single dose of Afluria QIV on 9/29/15 and had onset of Grade 1 pyrexia on 9/30/15. Actual temperature was not recorded on the solicited AE diary page but "slight fever" was reported as an unsolicited AE. Subject #8400397-0072, Comparator QIV, two dose treatment group, 5-8 year age stratum, received the second vaccination on 11/13/15, and reported Grade 2 pyrexia on 11/17/15 through 11/19/15. The subject's parents reported this event as an unsolicited AE ("Other Body Symptom" diary page) but also entered Grade 0 fever and normal temperatures for all 7 days following the second vaccination (11/13/15 through 11/19/15) in the Solicited AE diary. In response to our IR, the Applicant explained that the discrepant entries were not addressed with the parents, and that they took a conservative approach, analyzing the events as reported (both Grade 2 pyrexia as an unsolicited AE and Grade 0 temperatures for the same days as solicited AEs) in the final analysis. The Applicant's decision not to include the

two apparent cases of severe (Grade 3) and moderate (Grade 2) fevers in the final analyses of Solicited AEs appears reasonable because actual temperatures were not recorded and verbal recall was not allowed by the protocol. Additionally, inclusion of another case of solicited severe fever (n=3) among subjects 5-8 years who received Comparator QIV (n=274) would have resulted in a solicited severe fever rate of 1.1% rather than 0.7%, as compared to the rate of 1.2% in Afluria QIV recipients 5-8 years. Thus, the conservative approach taken by the Applicant did not favor or change our overall interpretation of the safety profile for Afluria QIV.

Reviewer comment: Although Afluria QIV recipients reported more Unsolicited AEs than Comparator QIV recipients overall (14.4% vs 12.0%, respectively), Comparator QIV recipients reported slightly higher rates of severe unsolicited AEs (0.5% vs 0.9%, respectively) and severe pyrexia (0.2% vs 0.4%, respectively). A total of 2 (0.1%) Afluria QIV recipients and 1 (0.2%) Comparator QIV recipient had severe unsolicited AEs assessed as related to study vaccine. Overall, the rates are low and comparable and do not raise new safety concerns.

Subpopulation Analyses of Unsolicited Adverse Events

Overall, rates of unsolicited AEs between males and females 5-17 years were similar in both treatment groups. In the 28 days following vaccination, a total of 14.8% and 13.9% of male and female recipients of Afluria QIV, respectively, and 11.4% and 12.6% of male and female recipients of Comparator QIV reported unsolicited AEs. Similar to overall rates, no large differences between males and females were observed in the rates of AEs as categorized by SOC. For additional information, please refer to CSLCT-QIV-13-02 CSR Table 14.3.1.7.3.1 (STN 125254/642.5).

Sub-analyses of racial groups revealed a trend towards lower overall rates of unsolicited AEs in blacks/African Americans, who comprised 20.7% of the Overall Safety Population, as compared to whites. Overall rates of unsolicited AEs in black/African Americans vs white Afluria QIV recipients were 11.7% and 15.3%, respectively, and, among Comparator QIV recipients, 9.1% and 13.0%, respectively. Among Afluria QIV recipients, the largest disparities in rates of AEs between blacks/African Americans and whites, respectively, were observed in the SOC categories of Infections and Infestations (2.9% vs 5.3%) and General Disorders and Administration Site Conditions (2.3% vs 3.4%). Small sample sizes precluded meaningful sub-analyses of unsolicited AEs in other racial groups. For additional information, please refer to CSLCT-QIV-13-02 CSR Table 14.3.1.7.4.1 (STN 125254/642.5).

Hispanic/Latinos comprised 23.8% of the OSP. Overall rates of unsolicited AEs among Afluria QIV recipients were lower in Hispanic/Latinos as compared to non-Hispanic/Latinos (10.6% vs 15.6%) whereas rates among Comparator QIV recipients were higher in Hispanic/Latinos as compared to non-Hispanic/Latinos (14.7% vs 11.2%). The greatest differences between Hispanic/Latinos and non-Hispanic/Latinos, respectively, among Afluria QIV recipients occurred in the following SOCs: Infections and Infestations (2.7% vs 5.3%); Respiratory, Thoracic, and Mediastinal Disorders (3.4% vs 4.3%); and General Disorders and Administration Site Conditions (1.5% vs 3.7%). For additional information, please refer to CSLCT-QIV-13-02 CSR Table 14.3.1.7.5.1 (STN 125254/642.5).

Reviewer comment: Subpopulation analyses in Afluria QIV recipients showed trends towards higher rates of unsolicited AEs in whites as compared to

blacks/African Americans and in non-Hispanic/Latinos as compared to Hispanic/Latinos. No clear trends were observed in subanalyses according to sex. Review of CSLCT-QIV-13-01, the study of Afluria QIV in adults ≥18 years also showed trends towards higher rates of unsolicited AEs in whites and non-Hispanics vs blacks/African Americans and Hispanic/Latinos (please see the clinical review of STN 125254/565 for details). However, neither of these studies was designed to detect significant differences between subpopulations, and one 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

In the 180 days following any vaccination, a total of 10 subjects, 8 (0.5%) Afluria QIV and 2 (0.4%) Comparator QIV recipients, reported 13 SAEs. Six of the 8 Afluria QIV subjects and both of the Comparator QIV recipients were in the 9-17 year age stratum. All but two SAEs occurred during the long-term follow-up period, i.e., more than 28 days after the final vaccination. Table 19 summarizes all SAEs that occurred from Day 1 through 180 days post-vaccination by MedDRA SOC, PT, and treatment group.

Table 19: Frequency of Serious Adverse Events According to MedDRA System Organ Class, Preferred Term, and Treatment Group – Subjects 5 through 17 Years (Overall Safety Population) – CSLCT-QIV-13-02*

System Organ Class (SOC) • Preferred Term (PT)	**Afluria QIV N=1692 n(%)**	**Comparator QIV N=560 n(%)**	**Overall N=2252 n(%)**
≥1 SAE – 5-17 years	8 (0.5)	2 (0.4)	10 (0.4)
≥1 SAE – 5-8 years**	2 (0.2)	0	2 (0.2)
≥1 SAE – 9-17 years**	6 (0.7)	2 (0.7)	8 (0.7)
Infections and infestations	2 (0.1)	0	2 (<0.1)
• Gastritis viral	1 (<0.1)	0	1 (<0.1)
• Influenza	1 (<0.1)	0	1 (<0.1)
Psychiatric disorders	4 (0.2)	1 (0.2)	5 (0.2)
• Depression***	1 (<0.1)	0	1 (<0.1)
• Attention deficit /hyperactivity disorder	1 (<0.1)	0	1 (<0.1)
• Bipolar disorder	1 (<0.1)	0	1 (<0.1)
• Psychotic disorder	1 (<0.1)	0	1 (<0.1)
• Suicidal ideation	1 (<0.1)	0	1 (<0.1)
• Suicide attempt	0	1 (0.2)	1 (<0.1)
Gastrointestinal disorders	1 (<0.1)	0	1 (<0.1)
• Abdominal pain	1 (<0.1)	0	1 (<0.1)
Pregnancy, puerperium and perinatal conditions	0	1 (0.2)	1 (<0.1)
• Abortion spontaneous	0	1 (0.2)	1 (<0.1)
Injury, poisoning, and procedural complications	2 (0.1)	0	2 (<0.1)
• Femur fracture	1 (<0.1)	0	1 (<0.1)
• Pancreatic injury	1 (<0.1)	0	1 (<0.1)

Source: Adapted from STN 125254/642, Module 5, CSLCT-QIV-13-02 CSR, Tables 12.3.2, 14.3.1.10.1 and 14.3.1.10.2, and the electronic datasets.
*ClinicalTrials.gov identifier: NCT02545543
**Percentages based on number of subjects in the respective treatment groups of the Overall Safety Population of subjects 5-17 years. Denominators for subjects 5-8 years: Afluria QIV n=865; Comparator QIV n=286; Overall n=1151. Denominators for subjects 9-17 years: Afluria QIV n=827; Comparator QIV n=274; Overall n=1101.
***Subject 8400390-0053 had two separate SAEs of depression but appears once in the table. All other PTs occurred as single SAEs.

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 and adolescent population, in particular, psychiatric disorders which occurred in six of the ten subjects (7 of 13 SAEs). No large imbalances were observed between treatment groups.

Table 20 lists the 13 SAEs experienced by 10 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, however, the Applicant considered an SAE of influenza as fulfilling criteria for vaccine failure and, therefore, related.

Table 20: SAEs Day 1 through Day 180 by Treatment, Age Group, and Subject (Overall Safety Population) – CSLCT-QIV-13-02*

Treatment Group	Age Group	Subject	Preferred Term	Onset[1]	Severity Grade[2]	Related[3]	Outcome
Afluria QIV	5-8 yrs	289-0087	Influenza	140	Grade 2	No[4]	Resolved
Afluria QIV	5-8 yrs	383-0063	Abdominal pain	174	Grade 2	No	Resolved
Afluria QIV	9-17 yrs	282-0009	Attention deficit hyperactivity disorder	88	Grade 3	No	Not resolved
Afluria QIV	9-17 yrs	282-0009	Bipolar disorder	88	Grade 3	No	Not resolved
Afluria QIV	9-17 yrs	390-0053	Depression	58	Grade 3	No	Resolved
Afluria QIV	9-17 yrs	390-0053	Exacerbation of depression	71	Grade 3	No	Resolved/ Sequelae
Afluria QIV	9-17 yrs	293-0005	Femur fracture	61	Grade 3	No	Resolved/ Sequelae
Afluria QIV	9-17 yrs	386-0028	Pancreatic injury	25	Grade 3	No	Resolved
Afluria QIV	9-17 yrs	399-0018	Gastritis viral	33	Grade 2	No	Resolved
Afluria QIV	9-17 yrs	399-0018	Psychotic disorder	77	Grade 2	No	Resolved
Afluria QIV	9-17 yrs	395-0037	Suicidal ideation	168	Grade 2	No	Resolved
Comparator QIV	9-17 yrs	317-0008	Suicide attempt	19	Grade 3	No	Resolved
Comparator QIV	9-17 yrs	386-0032	Abortion spontaneous	87	Grade 3	No	Resolved

Source: Adapted from STN 125254/642, Module 5, CSLCT-QIV-13-02 CSR, Tables 12.3-2, 14.3.1.10.1, and 14.3.1.10.2, case narratives, and the electronic datasets.
*ClinicalTrials.gov identifier: NCT02545543
[1]Onset = Number of days following most recent study vaccination 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.
[4]Assessed as not related by investigator but as fulfilling criteria for vaccine failure (related) by Applicant.

Reviewer comment: Case narratives and case report forms (CRFs) for each SAE were reviewed. The reviewer agrees with the Applicant and investigators' assessments that, with the exception of the case of influenza B infection, 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. The reviewer agrees with the Applicant's assessment that the case of influenza B may be considered a vaccine failure and, in that context, related. Two SAEs of interest are briefly summarized below, the case of influenza B (Afluria QIV recipient) and a spontaneous abortion (Comparator QIV recipient).

- Subject 8400289-0087 was a 5-year old white male whose medical history included prior influenza vaccination in August 2014, hives, chronic constipation

treated with daily macrogol, developmental delay, "hypoglycemic spells", and a "suspected genetic disorder". He received Afluria QIV on October 8, 2015. In February 2016 he developed rhinorrhea, nausea, vomiting, diarrhea, abdominal pain, and low grade fever. He was hospitalized on (b) (6) for dehydration, hypoglycemia (glucose 48), and nondiabetic metabolic ketoacidosis, tested positive for influenza B, and was treated with ondansetron and IV fluids. He recovered and was discharged. The SAE was assessed as moderate in severity and not related to study vaccine by the investigator. The Applicant considered the SAE as representing vaccine failure and, therefore, related to study vaccine.

- Subject 8400386-0032 was an 18-year old female with a history of acne, environmental allergies, and influenza vaccination in 2013. She received Comparator QIV on September 27, 2015, and experienced a spontaneous abortion, dilation and curettage on (b) (6). Her last menstrual period was on October 10, 2015, estimated due date July 10, 2016, no adverse findings on pre-natal testing. This was her first pregnancy. Outcome was reported as recovered on December 17, 2015. The event was assessed as severe, serious (medically significant), and not related to study vaccine.

Reviewer comment: The Applicant calculated the exposure to study vaccine as being ~4 weeks prior to the last menstrual period and ~7 weeks prior to conception. First trimester spontaneous abortions are relatively common and mostly due to embryonic causes. The rate of spontaneous abortion in early pregnancy (<20 weeks gestation) in females <35 years of age is approximately 15%. Rates are higher in the first trimester and in first pregnancies. Rates increase with maternal age, are higher in females with risk factors such as prior miscarriage and smoking, and are higher in studies where clinically unrecognized pregnancy was diagnosed by measuring daily urine HCG levels. There is no known association between inactivated influenza vaccines and spontaneous abortion. Influenza vaccination is recommended in pregnant females because they are at greater risk for complications of influenza infection. A pregnancy registry will be established for Afluria QIV. [1,3,8,48]

Subpopulation Analyses of Serious Adverse Events

Subpopulation analyses of SAEs in Afluria QIV recipients revealed higher proportions of SAEs in males (0.7%) vs females (0.2%) and non-Hispanic/Latinos (0.6%) vs Hispanic/Latinos (none). Rates in blacks (0.6%) and whites (0.5%) were similar. SAEs were not reported among other racial groups.

Reviewer comment: Subpopulation analyses of SAEs according to sex and ethnicity revealed a very small imbalance or trend towards more SAEs in male and non-Hispanic/Latino recipients of Afluria as compared to females and Hispanic/Latinos. However, the small number of SAEs overall precluded meaningful interpretation of these data.

6.1.12.5 Adverse Events of Special Interest (AESI)

No AESIs were reported by the Applicant during this study (see Section 6.1.7 for definition and monitoring plan). Evaluation of the electronic datasets confirmed the Applicant's report.

Reviewer comment: Although not defined as an AESI by Seqirus Pharmacovigilance, the Applicant conducts routine postmarketing surveillance for severe injection site reactogenicity. A case of cellulitis-like reaction following vaccination with Afluria QIV occurred in study CSLCT-QIV-13-02, and is of interest (see Section 6.1.12.2). The review team accepted the Applicant's rationale for continuing to categorizing "large/extensive injection site swelling and cellulitis-like reaction" as important potential risks (please see Section 4.6).

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 hypotension episodes or anaphylaxis in the 30 minutes post-vaccination.

6.1.12.7 Dropouts and/or Discontinuations

Overall, 95.3% and 94.0% of Afluria QIV and Comparator QIV recipients completed the study, and 98.9% provided at least some evaluable safety follow-up data. None of the total 5.0% 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 HI GMT and SCR co-primary endpoints and pre-specified non-inferiority criteria for 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 5 through 17 years.

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. Except for the B/Yamagata strain in children 5-8 years, Afluria QIV met immune response criteria commonly used to evaluate influenza vaccines. Children 5-8 years missed the % HI ≥1:40 endpoint for B/Yamagata by a very small margin in both treatment groups.

Statistically significantly lower pre- and post-vaccination HI GMTs and % HI ≥1:40 were observed for the B virus strains relative to the A strains, and may reflect lower rates of prior wild type or vaccine exposure to influenza B antigens, especially in the younger age cohort. However, a pattern of lower responses to B strains is not unusual for influenza vaccines, and Afluria QIV demonstrated non-inferior immunogenicity relative to the comparator.

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 and age cohort. Subgroup analyses of GMTs, % HI ≥1:40, and SCRs conducted for white and black race and Hispanic/Latino and non-Hispanic/Latino ethnicity were similar between

treatment groups and, for Afluria QIV recipients, showed a statistically significant trend (non-overlapping 95% CIs) towards higher post-vaccination GMTs for A/H1N1 and A/H3N2 in blacks as compared to whites, and non-statistically significant (overlapping 95% CIs) lower SCRs in Hispanic/Latinos as compared to non-Hispanic/Latinos. Immune responses were otherwise similar between sex, race and ethnic groups. Subanalyses of non-inferiority showed that GMT ratios and SCR differences between sexes, blacks and whites, and Hispanic/Latinos and non-Hispanic/Latinos were not statistically significantly different. The clinical significance of these observations is uncertain 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.

Safety Conclusions

Safety data following administration of Afluria QIV to healthy subjects 5 through 17 years suggested no serious concerns and were generally comparable to a U.S.-licensed QIV. No subjects died during the 6-months following vaccination. No discontinuations (Afluria QIV 4.7%, Comparator QIV 6.0%) were due to AEs.

In the 180 days following any vaccination, a total of 10 subjects, 8 (0.5%) Afluria QIV and 2 (0.4%) Comparator QIV recipients, reported 13 SAEs. Six of 8 Afluria QIV recipients and both Comparator QIV recipients with SAEs were in the 9-17 year age stratum. Most SAEs occurred >28 days post-vaccination and were common diagnoses in a pediatric and adolescent population. With the exception of a case of influenza B infection that may be considered a vaccine failure and in that context related, 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.

Among Afluria QIV and Comparator QIV recipients 5 through 8 years, 57.2% and 54.0%, respectively, reported solicited local reactions, primarily injection site pain (51.3% and 49.6%, respectively). Afluria QIV recipients reported slightly higher rates of local swelling as compared to Comparator QIV (15.3% vs 12.4%, respectively), and slightly higher rates of severe swelling (3.4% vs 2.2%, respectively) and severe redness (3.5% vs 1.8%, respectively). Most reactions were mild to moderate in severity and resolved within 2 days. Among subjects who received two doses, rates of all local reactions and severe reactions were lower following the second dose, although the overall rates of local swelling declined to a lesser extent following the second vaccination with Afluria QIV (Dose 1 = 14.0%, Dose 2 = 11.2%) as compared to Comparator QIV (Dose 1 = 12.5%, Dose 2 = 4.8%). 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.

Among Afluria QIV and Comparator QIV recipients 9 through 17 years, 54.9% and 50.2%, respectively, reported solicited local reactions, primarily pain (51.5% vs 45.2%, respectively). Most reactions were mild in severity and resolved within 2 days. Overall rates of any severe local reactions were similar between treatment groups (Afluria QIV 3.2%, Comparator QIV 3.8%).

Among Afluria QIV and Comparator QIV recipients 5 through 8 years, 27.6% and 26.3%, respectively, reported solicited systemic AEs. The most frequently reported symptoms (range 5.8% to 12.3%) were headache, myalgia, malaise/fatigue, and nausea, with only

small imbalances between treatment groups. Fever was uncommon, but overall rates of fever among Afluria QIV recipients were slightly higher than Comparator QIV recipients (4.5% vs 3.6%, respectively) as were rates of severe (Grade 3) fever (≥102.2°F or ≥39.0°C) (1.2% vs 0.7%). Most solicited systemic AEs were mild to moderate in severity. A total of 1.6% and 1.5% of Afluria QIV and Comparator QIV recipients, respectively, had severe systemic AEs (predominantly fever). The duration of most events was <2 days.

Among subjects 5-8 years who received two vaccinations, rates of solicited systemic AEs following the second vaccination were lower than the first vaccination in both treatment groups. Fever occurred in 4.0% and 3.0% of Afluria QIV and Comparator QIV recipients, respectively, after the first vaccination and in 2.2% and 3.2%, respectively, after the second vaccination. No subjects in either treatment group reported severe solicited systemic AEs, including fever, following the second vaccination.

Among Afluria QIV and Comparator QIV recipients 9 through 17 years, 34.1% and 28.7%, respectively, experienced solicited systemic AEs. The most frequently reported events occurred at higher rates in Afluria QIV recipients relative to Comparator QIV: headache (18.8% vs 14.6%), myalgia (16.7% vs 11.1%), and malaise/fatigue (10.0% vs 7.7%). Fever was uncommon but a small imbalance was observed between treatment groups, 2.1% vs 0.8% of Afluria QIV and Comparator QIV recipients, respectively. Severe solicited systemic AEs were uncommon, occurring in 1.4% and 0.8% of Afluria QIV and Comparator QIV, respectively. Severe (Grade 3) fever (≥102.2°F or ≥39.0°C) occurred in 0.5% of Afluria QIV recipients and in none of the comparator recipients. The duration of events was similar between treatment groups.

A total of 310 subjects (13.8%) 5 through 17 years reported 503 unsolicited AEs in the 28 days following vaccination, with a slighter higher proportion of Afluria QIV recipients (14.4%) reporting unsolicited AEs as compared to Comparator QIV (12.0%). However, the differences were small, with no large imbalances or unusual patterns of specific events, and did not appear clinically significant.

Overall, the rates of local injection site reactions observed in this study, including slightly higher rates among all subjects 5-8 years relative to 9-17 years, and higher rates of severe reactions among recipients of Afluria QIV relative to Comparator QIV, were acceptable. Small imbalances between treatment groups in rates of various solicited systemic AEs among children 5-8 years did not suggest significant concerns. Rates of fever and severe fever after any vaccination in children 5-8 years were slightly higher among Afluria QIV recipients (4.5 % and 1.2%, respectively) as compared to Comparator QIV (3.6% and 0.7%, respectively), but did not appear clinically significant, and were lower than historical rates for Afluria (trivalent formulation) in this age group (please see Section 2.4). Among subjects 9-17 years, Afluria QIV recipients experienced slightly more headache, myalgia, malaise/fatigue and fever following vaccination, with more rapid onset of fever, than the comparator group. However, the rates of systemic AEs were not unusually high and did not appear clinically significant. Additionally, rates of severe solicited systemic AEs in subjects 9-17 years were low and similar between treatment groups. The relatively small imbalances in solicited local and systemic AE data indicate that Afluria QIV was slightly more reactogenic than the comparator in a pediatric population 5-17 years, but that the frequency and severity of solicited AEs were clinically acceptable.

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-13-02 was associated with less pyrogenicity relative to historical rates. No febrile seizures were observed in this study. Postmarketing surveillance following approval may help determine whether the slightly higher but acceptable rates of local and systemic reactogenicity following administration of Afluria QIV as compared to Comparator QIV observed in this study are generalizable to a broader pediatric population 5-17 years or to future vaccine formulations containing different antigens.

Overall, subpopulation analyses of solicited AEs in Afluria QIV recipients showed higher rates in females, whites, and non-Hispanic/Latinos as compared to males, blacks/African Americans, and Hispanic/Latinos. Subpopulation analyses unsolicited AEs in Afluria QIV recipients showed trends towards higher rates in whites and non-Hispanic/Latinos as compared to blacks/African Americans and Hispanic/Latinos. No clear trends in unsolicited AEs were observed according to sex. Because the study was not designed to detect statistically significant differences between subpopulations, we cannot draw firm conclusions from the observed trends.

7. INTEGRATED OVERVIEW OF EFFICACY

The application supporting licensure of Afluria QIV in the pediatric population 5 through 17 years consisted of one study; integrated analyses of efficacy are not applicable.

8. INTEGRATED OVERVIEW OF SAFETY

The application supporting licensure of Afluria QIV in the pediatric population 5 through 17 years 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

Pregnant females were not eligible to enroll in study CSLCT-QIV-13-02. The Applicant provided case narratives for the three subjects, all Afluria QIV recipients, who became pregnant following exposure to study vaccine (STN 125254/642.1). Subjects 8400317-0011, 8400383-0006, and 8400386-0032 had negative pregnancy tests immediately prior to vaccination, and were subsequently diagnosed as being pregnant with exposures to Afluria QIV occurring during the first trimester. Of the three pregnancies, subject #8400317-0011 delivered a live infant with no reported abnormalities, subject #8400383-0006 had an elective termination with no fetal abnormalities reported, and subject #8400386-0032 had a spontaneous abortion. The spontaneous abortion was reported as an SAE (medically significant). Please see Section 6.1.12.4 for details.

No other human clinical trial safety data in pregnant or lactating females are currently available for Afluria QIV. A developmental toxicity study in rats, conducted with Afluria TIV, revealed no evidence of vaccine-related harm to the fetus. A Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) study of pregnant women exposed to Afluria TIV was recently completed and a final study report pending at the

time the clinical review was completed. As of the last Annual Report (IND 12997/141), six adverse outcomes were reported among 100 women exposed to Afluria TIV. The Applicant determined that the six cases involved co-suspect vaccines or medications and/or did not have strong pathophysiological mechanisms to support causality between Afluria TIV and the six adverse outcomes. Based on postmarketing experience with Afluria TIV and other inactivated influenza vaccines, no safety concerns have been identified regarding the use of Afluria QIV in pregnancy. Vaccination is recommended in pregnant women because they are at greater risk for complications of influenza infection. Vaccination of pregnant women may also protect infants in the first six months of life before they are eligible for vaccination. The Approval Letter for Afluria QIV in adults ≥18 years (STN 125254/565) includes a postmarketing commitment (PMC) for Seqirus to establish a pregnancy registry, a prospective observational study of pregnant women exposed to Afluria QIV, to assess exposure, safety, and outcomes in pregnancy. This study is scheduled to begin in the NH 2017-2018 influenza season in the U.S. Please see the OBE/DE review for additional information.

9.1.2 Use During Lactation

Please see Section 9.1.1.

9.1.3 Pediatric Use and PREA Considerations

Afluria TIV is approved in persons 5 years and older, and Afluria QIV was more recently approved in adults ≥18 years. Please see Section 2.5 for relevant regulatory history related to withdrawal of licensure in children 6 months to < 5 years due to increased postmarketing reports of febrile seizures and febrile events associated with the SH 2010 formulation of Afluria, and for a summary of interactions with the Pediatric Research Committee (PeRC) leading up to submission of the efficacy supplement for Afluria QIV in adults (STN 125254/565, study CSLCT-QIV-13-01). Due to concerns over pyrogenicity in children < 5 years of age, Seqirus conducted a small safety study (CSLCT-USF-10-69) of Afluria TIV in children 5 through 8 years of age concurrent with CSLCT-QIV-13-01 using (b) (4) the A/H3N2 and B strains. Because this study demonstrated acceptable safety including less pyrogenicity than in prior studies, CBER agreed that plans for a larger study of Afluria QIV in children 5 through 17 years of age (CSLCT-QIV-13-02) could proceed.

STN 125254/565, Afluria QIV in adults ≥18 years, triggered the Pediatric Research Equity Act (PREA) because it contained a new active ingredient (a second influenza type B virus antigen). Accordingly, the submission included a Pediatric Study Plan (PSP), and requests for a partial waiver and deferral of pediatric studies. Studies in children from birth to < 6 months of age were waived 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 (due to the immaturity of the neonatal immune system and interference from maternal antibodies). Assessments in two pediatric age groups were deferred because the product was ready for approval for use in adults and pediatric studies had not been completed. These postmarketing requirements (PMRs) and their associated timelines were as follows:

1. CSLCT-QIV-13-02, 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 and adolescents aged 5 through 17 years.

a. Final protocol submission: July 31, 2015
b. Study completion date: June 30, 2016
c. Final report submission: December 31, 2016

2. CSLCT-QIV-13-03, 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.
    a. Final protocol submission: July 31, 2016
    b. Study completion date: June 30, 2017
    c. Final report submission: December 31, 2017

The PeRC agreed with the Applicant's initial PSP, submitted to IND 15974, on September 3, 2014 and with the final PSP, submitted to STN 125254/565, on February 10, 2016.

Submission of the current efficacy supplement, STN 125254/642, required a PeRC review because the supplement contained data from a pediatric assessment in response to a PREA PMR. On April 5, 2017, the PeRC concurred with the review team's assessment that data from study CSLCT-QIV-13-02 support licensure of Afluria QIV in children and adolescents 5 through 17 years.

With approval of the current efficacy supplement STN 125254/642, Seqirus will fulfill the PMR to conduct a phase 3 study to evaluate the immunogenicity and safety of Afluria QIV in a pediatric population 5-17 years.

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 Aspects 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). (b) (4)

10. CONCLUSIONS

The immunogenicity and safety data from CSLCT-QIV-13-02 submitted to this efficacy supplement support traditional approval of Afluria QIV for use in children and adolescents 5 through 17 years.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 21 presents Risk-Benefit Considerations relating to approval of Afluria QIV in children and adolescents 5 through 17 years.

Table 21: Risk-Benefit Considerations		
Decision Factor	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition	• Influenza causes annual epidemics affecting ~5-20% of the population each year. Due to frequent mutations and reassortment, antigenic drift and shift, in viral envelope glycoproteins (HA and NA), 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 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 <18 years 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 pediatric populations (including 5-17 years) in the U.S. include: six trivalent (Afluria, Fluarix, FluLaval, Fluviron, Fluzone, and Flucelvax) and four quadrivalent (Fluarix, FluLaval, Fluzone, and Flucelvax) inactivated influenza vaccines (TIV and QIV), and a quadrivalent live-attenuated influenza vaccine (LAIV4) (FluMist Quadrivalent). Not all licensed products are manufactured and distributed in a given influenza season. • Approximately (b) (4) million doses of influenza vaccine were distributed in the U.S. in the 2016-2017 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 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 2016-2017 influenza season are less than the population for whom the vaccine is indicated.	• 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 TIV is ~60%-70% effective in preventing influenza illness. • Inclusion of both B lineages as part of a quadrivalent vaccine is projected to provide additional benefit in most seasons and is likely 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 2278 subjects 5 through17 years, vaccination with Afluria QIV elicited an immune response that met pre-specified HI GMT and SCR co-primary endpoints and success criteria for non-inferior 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 generally higher than responses to B strains in both treatment groups. • Subgroup analyses showed similar post-vaccination GMTs, % HI titers ≥1:40, and SCRs between sexes in each treatment group and age cohort. Subgroup analyses by race and ethnicity also showed similar immune responses with the exception of a statistically significant trend (non-overlapping 95% CIs) towards higher post-vaccination GMTs for A/H1N1 and A/H3N2 in black as compared to white recipients of Afluria QIV, and non-statistically significant (overlapping 95% CIs) lower SCRs 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 (STN 125254.259) .	• Non-inferior immunogenicity was demonstrated in subjects 5-17 years 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 of non-inferiority showed that GMT ratios and SCR differences 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	• In subjects 5-17 years, the most common AEs following any vaccination with Afluria QIV were mild to moderate local injection site pain, redness, and swelling, headache, myalgia, and malaise. Among subjects 5-8 years, solicited AEs following a second vaccination were less frequent than after the first dose. Most events resolved within 2 days. Overall rates of severe (Grade 3) solicited AEs (subjects 5-17 years) were low, similar between treatment groups (Afluria QIV 5.7%, Comparator QIV 4.7%), and comprised primarily of injection site reactions. Afluria QIV recipients 5-8 years had slightly higher rates of local swelling as compared to Comparator QIV (15.3% vs 12.4%) and severe local swelling (3.4% vs 2.2%) and severe redness (3.5% vs 1.8%) One cellulitis-like reaction (concurrent Grade 3 injection site pain, redness, and swelling) occurred in an 8-year old Afluria QIV recipient, and resolved without sequelae. Afluria QIV recipients 9-17 years had higher rates of solicited headache (18.8% vs 14.6%) and myalgia (16.5% vs 11.1%) as compared to Comparator QIV, but almost all of these events were mild to moderate. • Among subjects 5-8 years, fever ≥100.4°F occurred in 4.5% and 3.6%, and severe (Grade 3) fever (≥102.2°F or ≥39.0°C) in 1.2% and 0.7%,of Aluria QIV and Comparator QIV recipients, respectively. Rates following a second vaccination were lower (2.2% and 3.2%, respectively, overall). Fever was uncommon among subjects 9-17 years, but a small imbalance was observed between treatment groups (Afluria QIV 2.1%, Comparator QIV 0.8%). Severe fever occurred in 0.5% of Afluria QIV recipients and no comparator recipients 9-17 years. No febrile seizures were reported in either age or treatment group. • No subjects died or were discontinued due to AEs in the six months post-vaccinations. SAEs were uncommon (Afluria QIV 0.5%, Comparator QIV 0.4%). Most SAEs occurred >28 days post-vaccination and were common diagnoses in a pediatric population. Other than a case of influenza B infection that may be considered a vaccine failure and in that context related, no SAEs appeared related to study vaccines. • Subpopulation analyses showed that higher proportions of females reported solicited and	• The safety profile of Afluria QIV was comparable to a U.S.-licensed QIV and clinically acceptable. Small imbalances in solicited AEs, including fever, suggest that Afluria QIV was slightly more reactogenic than Comparator QIV, but the differences did not appear clinically significant. • Among subjects 5-8 years, rates of fever in the 7 days following vaccination with Afluria QIV were lower than historical rates for Afluria TIV. (b) (4) the four Afluria QIV vaccine virus strains used in study CSLCT-QIV-13-02 appear associated with less pyrogenicity. However, it is not clear whether the lower rates of fever observed in CSLCT-QIV-13-02 are generalizable to a broader population 5-17 years, younger children (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.

	unsolicited AEs as compared to males in both treatment groups, and trends towards lower rates of solicited local and systemic reactogenicity in blacks/African Americans as compared to whites (particularly among Afluria QIV recipients), and among Hispanics/Latinos as compared to non-Hispanics/Latinos. • Safety was not evaluated in pregnant women or nursing mothers.	
Risk Management	• A cellulitis-like reaction occurred in the clinical trial. "Large/extensive injection site swelling" and "cellulitis-like reactions" are classified as important potential risks in the PVP. • Any potential for increased local and systemic reactogenicity, including febrile reactions, associated with Afluria QIV can be further described in postmarketing surveillance. • No new or unexpected safety signals were apparent in subjects 5-17 years. 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 will establish a pregnancy registry for Afluria QIV.	• The Applicant continually monitors clinical and postmarketing data for 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. • Please see the OBE/DE review for details of the postmarketing pregnancy study.

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 5 through 17 years, 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. Small imbalances in solicited AEs, including fever, suggest that Afluria QIV was slightly more reactogenic than the comparator, however, the differences did not appear clinically significant because overall rates were low and no events were serious. No febrile seizures were reported in the study. Notably, rates of fever among subjects 5-8 years, in the 7 days following vaccination with Afluria QIV were lower than historical rates for Afluria TIV. 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, (b) (4) the four Afluria QIV vaccine virus strains used in study CSLCT-QIV-13-02 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 5 through 17 years. Routine postmarketing surveillance appears sufficient and will help clarify whether the lower rates of fever observed in CSLCT-QIV-13-02 are generalizable to a broader population 5-17 years 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 5 years and older. Please see Section 11.1.

11.4 Recommendations on Regulatory Actions

From the clinical perspective, data from CSLCT-QIV-13-02 support traditional approval of Afluria QIV in children and adolescents 5 through 17 years. Rates of febrile seizures (zero), febrile events, and severe injection site reactions 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 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 5 through 17 years and a dosing

regimen of one or two doses at least one month apart for children 5 through 8 years as indicated based on prior vaccination history.

- Highlights and Adverse Reactions [6.1]: Added safety data from CSLCT-QIV-13-02 in persons 5-17 years.
- Clinical Studies [14]: Added immunogenicity data from CSLCT-QIV-13-02 in persons 5-17 years.
- Highlights, Pregnancy [8.1], and Patient Counseling Information [17]: Updated with contact information for the pregnancy registry.

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

11.6 Recommendations on Postmarketing Actions

The review team recommended no additional PMCs or PMRs beyond those already outlined in the August 26, 2016 Approval Letter for Afluria Quadrivalent. These include an ongoing Phase 3 study of Afluria QIV in a pediatric population 6 months through 59 months (CSLCT-QIV-15-03) and a pregnancy registry. Please see Sections 1, Executive Summary, and 9.1, Special Populations, and the OBE/DE review for details.