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BLA Clinical Review Memorandum

Application Type	Supplemental Biologics License Application
STN	103914\6208
CBER Received Date	30 March 2018
PDUFA Goal Date	28 January 2019
Division / Office	Division of Vaccines and Related Product Applications/ Office of Vaccine Research and Review
Priority Review (Yes/No)	No
Reviewer Name(s)	Susan K. Wollersheim, MD
Review Completion Date / Stamped Date	
Supervisory Concurrence	Roshan Ramanathan, MD, MPH, Acting Branch Chief, Clinical Review Branch 1
Applicant	Sanofi Pasteur
Established Name	Influenza Virus Vaccine
(Proposed) Trade Name	Fluzone Quadrivalent
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Liquid suspension for intramuscular injection **Antigens** Each 0.25mL and 0.5mL vaccine dose contains 7.5 µg and 15µg HA, respectively, of each antigen: A/California/07/2009 X-179A (H1N1) A/Hong Kong/4801/2014 X-263B (H3N2) B/Brisbane/60/2008 (Victoria lineage; B1) B/Phuket/3073/2013 (Yamagata lineage; B2) **Other ingredients:** • Sodium phosphate-buffered isotonic sodium chloride solution • Formaldehyde • Octylphenol Ethoxylate • Thimerosal (multi-dose presentation only)
Dosage Form(s) and Route(s) of Administration	Suspension for intramuscular injection Supplied in three presentations: • 0.25 mL prefilled single-dose syringe (for persons 6 to < 36 months of age • 0.5 mL prefilled single-dose syringe (for persons 6 months of age and older)

	• 0.5 mL single-dose vial (for persons 6 months of age and older) • 5 mL multi-dose vial (for persons 6 months of age and older)
Dosing Regimen	• Ages 6 to < 36 months: 1 or 2 doses*, 0.25mL each. If 2 doses, administer at least 4 weeks apart. • Ages 36 months to < 9 years: 1 or 2 doses*, 0.5mL each. If 2 doses, administer at least 4 weeks apart. • Age 9 years and older: 1 dose, 0.5mL. * 1 or 2 doses depends on vaccination history as per Advisory Committee on Immunization Practices annual recommendations on the prevention and control of influenza with vaccines.
Indication(s) and Intended Population(s)	Fluzone Quadrivalent is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. Fluzone Quadrivalent is approved for use in persons 6 months of age and older. The purpose of this efficacy supplement is to support the use of a 0.5mL dose in children 6 to <36 months of age. The indication is unchanged.
Orphan Designated (Yes/No)	No

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GLOSSARY

ACIP	Advisory Committee on Immunization Practices
AE	Adverse event
AR	Adverse reaction
BIMO	CBER Bioresearch Monitoring
BL	Blood sample
BLA	Biologics license application
BPCA	Best Pharmaceuticals for Children Act
CFR	Code of Federal Regulations
CMC	Chemistry, manufacturing, and controls
DC	Diary card
FDA	Food and Drug Administration
GMT	Geometric Mean Titer
HA	Hemagglutinin
HAI	Hemagglutination inhibition
HCP	Health care provider
IIV	Inactivated influenza vaccine
IR	Information request
LL	Lower Limit
MedDRA	Medical Dictionary for Regulatory Activities
NA	Neuraminidase
OBE	Office of Biostatistics and Epidemiology
OVRR	Office of Vaccines Research and Review
PeRC	Pediatric Review Committee (CDER)
PP	Per-protocol Analysis Set
PREA	Pediatric Research Equity Act
QIV	Quadrivalent influenza vaccine
SAE	Serious adverse event
SAS	Safety Analysis Set
SD	Standard deviation
SOC	System organ class
STN	Submission tracking number
sBLA	Supplemental biologics application
SC	Seroconversion
SCR	Seroconversion rate
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. Executive Summary

Fluzone Quadrivalent inactivated influenza vaccine (QIV) is currently licensed for the prevention of influenza in persons 6 months of age and older; currently the volume of a single dose in children 6 to < 36 months of age is 0.25 mL, and in persons 3 years of age and older, the volume of a single dose is 0.5 mL. With this supplement, Sanofi Pasteur is seeking approval for use of 0.5 mL per dose in all persons 6 months of age and older.

Summary of Clinical Findings
Study GRC88 was a Phase IV, randomized, observer-blinded, 2-arm, multi-center (38 U.S. centers) study to evaluate the safety and immunogenicity of 2 different dose levels of Fluzone Quadrivalent influenza vaccine in healthy children 6 to < 36 months of age. A total of 1950 subjects were randomly assigned in a 1:1 ratio to either 1 of the 2 groups: Group 1 [0.25 mL per dose of Fluzone Quadrivalent vaccine (n=955)] or Group 2 [0.5 mL per dose of Fluzone Quadrivalent vaccine (n=995)]. Randomization was stratified by center and age (6 to <24 months and 24 to <36 months). Among the 1950 randomized subjects, 1460 (74.9%) were randomly assigned to the immunogenicity subset: 715 subjects in Group 1 and 745 subjects in Group 2. Subjects received either 1 or 2 dose(s) of Fluzone Quadrivalent vaccine based on the recommendation of the Advisory Committee on Immunization Practices (ACIP) guidance.

The primary objective of this study was to compare the rate of any fever (temperature ≥ 100.4°F [38.0°C]) in Group 2 to that of Group 1 during the 7 days after either vaccination (Dose 1 and Dose 2 combined) in subjects 6 to < 36 months of age. Non-inferiority was demonstrated if the upper limit of the 2-sided 95% confidence interval (CI) of the fever rate difference (Group 2 - Group 1) was < 5%.

The fever rate of Group 2 (12.15%) was not statistically significantly higher than the fever rate of Group 1 (11.31%) according to the pre-specified safety criterion for non-inferiority; the difference in fever rates was 0.84% (95% CI: -2.1%; 3.8%).

Safety data showed that solicited local adverse reactions and systemic adverse reactions (with the exception of fever) experienced by subjects in Group 2 occurred at similar rates compared with Group 1. No imbalances in the frequency or severity of unsolicited adverse events were observed between the treatment arms, and serious or uncommon conditions were not observed at unexpectedly high frequencies in any group.

A total of 10 serious adverse events were reported (5 in each group), and 1 SAE (chronic urticaria) in Group 1 was described as vaccine related by the applicant. No deaths were reported.

The secondary objective of this study was to compare antibody responses between the treatment arms as assessed by the ratio of Geometric Mean Titers (GMTs) and Seroconversion rate (SCR) differences after the final vaccination in subjects 6 to < 36 months of age. Non-inferiority criteria were met provided: (a) the lower limit (LL) of the 2-sided 95% CI of the GMT ratio ($GMT_{0.5mL}$ / $GMT_{0.25mL}$) was > 0.67 for each of the 4 virus strains, and (b) the LL of the 2-sided 95% CI of the difference in SCRs ($SCR_{0.5mL}$ minus $SCR_{0.25mL}$) was > -10% for each of the 4 virus strains contained in the vaccine.

Group 2 antibody responses were non-inferior to Group 1 antibody responses according to the pre-specified non-inferiority immunogenicity criteria, with respect to all 4 strains contained in the vaccine. GMT ratios ($GMT_{0.5\text{-mL}}$ divided by $GMT_{0.25\text{-mL}}$) for the A/H1N1, A/H3N2, B Victoria lineage, and B Yamagata lineage strains were 1.42 (95% CI: 1.16; 1.74), 1.48 (95% CI: 1.21; 1.82), 1.33 (95% CI: 1.09; 1.62), and 1.41 (95% CI: 1.17; 1.7), respectively. Seroconversion rate (SCR) differences ($SCR_{0.5\text{-mL}}$ minus $SCR_{0\ 25\text{-mL}}$) for the A/H1N1, A/H3N2, B Victoria lineage, and B Yamagata lineage strains were 4.6% (95% CI: -0.4%; 9.7%), 5.1% (95% CI: 0.4%; 9.8%), 1.3% (95% CI: -2.9%; 5.6%), and 2.6% (95% CI: -1.4%; 6.5%).

Data submitted to sBLA 103914\6208 establish likelihood of benefit of the 0.5 mL dose volume of Fluzone Quadrivalent in children 6 to < 36 months of age. The risks of vaccination with the 0.5 mL dose volume of Fluzone Quadrivalent in children 6 to < 36 months of age were minimal and similar to the risks of vaccination with the previously approved 0.25 mL dose volume. Thus, the overall risk/benefit profile of the 0.5 mL dose volume is favorable in this age group.

Compliance with Pediatric Research Equity Act (PREA)
Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), an assessment of the safety and effectiveness of the product for the claimed indication in all pediatric age groups must be submitted at the time an application for a new active ingredient is submitted, unless the requirement for assessment has been deferred or waived. A waiver from conducting studies with QIV in children from birth to <6 months of age was granted because available data in infants in this age group indicate that serum antibody responses to inactivated influenza vaccines are not as robust as in older children, likely due to the inherent immaturity of the immune system and interference from maternal antibody. Thus, use of Fluzone Quadrivalent in infants <6 months of age would provide no meaningful therapeutic benefit over initiating vaccination at 6 months of age, and the vaccine is not likely to be used in a substantial number of infants < 6 months of age.

Recommendation for Regulatory Action
The clinical data submitted by the Applicant support the approval of the 0.5 mL dose of Fluzone Quadrivalent for active immunization of children 6 to < 36 months of age against influenza disease caused by the influenza subtypes A and type B viruses contained in the vaccine.

Recommendation on Postmarketing Action
No postmarketing requirement for additional safety studies is necessary beyond routine pharmacovigilance.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The study was not powered to detect differences in immunogenicity or safety with regard to age, gender or geographical ancestry. Post hoc subgroup analyses of immunogenicity and safety were performed by age, gender, and ethnicity. The subgroup analyses of immunogenicity and safety by age, gender, and ethnicity generally were shown to be consistent with the overall immunogenicity and safety results.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Influenza is an acute, highly contagious, respiratory disease condition caused by influenza viruses, mainly spread through respiratory droplets. The illness is accompanied by fever and variable degrees of other systemic symptoms, ranging from mild fatigue to respiratory failure and even death. Influenza occurs in annual epidemics that are associated with significant morbidity and mortality and have substantial public health impact. Annual influenza epidemics are responsible for an estimated 3 to 5 million cases of severe illness and 290,000 to 650,000 respiratory deaths worldwide annually (1). The highest risk of complications occurs among children under 5 years, adults 65 years of age or older, pregnant women, and people of any age with underlying chronic conditions (1).

The highest influenza burden in terms of pediatric respiratory admissions is seen in infants 6 through 11 months of age (2), and rates of illness in children younger than 2 years of age are substantially higher than those in children 2 years of age or older (3, 4). Children also play an important role in the spread of the disease (5), possibly because of their high levels of virus shedding. Because annual influenza vaccination is currently the most effective means of controlling influenza and preventing its complications and mortality (6), it is recommended for all people 6 months of age and older.

Influenza A H1N1, A H3N2 and B viruses have co-circulated in the community since the late 1970s, and from that time seasonal influenza vaccines have contained three influenza strains, one from each A subtype and one type B virus (7). Since 1985, two antigenically distinct lineages of influenza B viruses (Victoria or Yamagata lineages) have co-circulated globally and have caused extensive illness, particularly in children, as limited cross protection is provided against strains in the B lineage not contained in the trivalent vaccine (7, 8). Because of difficulty predicting which influenza B lineage will be predominantly circulating resulting in frequent seasonal mismatches for the influenza B strain, quadrivalent influenza vaccines (QIV) have been developed which include both influenza B lineages.

There is no established immune correlate of protection for influenza. However, experimental influenza challenge studies in humans suggest that serum hemagglutination inhibiting antibody titers of 1:40 are associated with protection against illness in up to 50% of subjects (9).

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

Prevention of influenza disease can be achieved through vaccination or the use of antiviral medication. Two classes of antivirals against influenza, the adamantanes and the neuraminidase inhibitors, have been approved for both treatment and prevention (pre-exposure chemoprophylaxis). Use of drugs in the adamantane class is no longer recommended due to widespread resistance among circulating influenza virus strains. Although neuraminidase inhibitors are currently effective against most seasonal influenza viruses, resistance to drugs in this class has developed sporadically (10), with most of the benefit derived when given prophylactically or early in the disease course.

2.3 Safety and Efficacy of Pharmacologically Related Products

Active immunization is the primary method for prevention of influenza. Vaccination appears to protect primarily through the induction of serum antibody directed against the Hemagglutinin (HA) and Neuraminidase (NA) surface proteins. These antibodies are subtype and strain-specific, and thus protect against identical or closely related strains, but not against other types or subtypes. As a result of antigenic evolution and a short duration of immunity, influenza vaccination must be received annually.

Inactivated whole-virus influenza vaccines have been commercially available since the 1940s, and results of large multicenter trials of whole virus influenza vaccines conducted in children during the 1970s demonstrated that a lower antigen dose resulted in improved tolerability of the whole virus vaccines (11).

Currently, eight inactivated split-virus influenza vaccines are licensed in the U.S., and all are currently approved for use in children 6 to < 36 months of age. They include: Fluzone, Fluzone Quadrivalent, Fluarix, Fluarix Quadrivalent, Flulaval, Flulaval Quadrivalent, Afluria and Afluria Quadrivalent.

Fluzone Quadrivalent was approved for use in individuals 6 months of age and older in June 2013 (reviewed in STN 103914\5574) for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. The dosing regimen for infants 6 to < 36 months of age currently is 0.25 mL containing 7.5 µg HA of each influenza viral strain compared with 15 µg HA per strain in a 0.5 mL dose indicated for persons 3 years of age and older. This difference in the dose volumes and antigen content was based primarily on the results of large multicenter trials of whole virus influenza vaccines conducted in children during the 1970s which demonstrated that a lower antigen dose resulted in improved tolerability of the whole virus vaccines (11). However, whole virus influenza vaccines are no longer available in the U.S., and seasonal inactivated influenza vaccines are prepared by chemically disrupting the virus to produce a split-virus which is better tolerated in children.

Flulaval and Flulaval Quadrivalent were approved for use in individuals 6 months of age and older in November 2016 (reviewed in STN 125163\405) for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. The volume of a single dose for persons 6 months of age and older is 0.5 mL; each dose contains 15 µg HA of each influenza viral strain. Fluzone Quadrivalent was the active comparator for the pivotal study to support licensure in infants and children 6 months through 35 months of age. One of the safety endpoints of this pivotal study was the relative risk of fever following Flulaval QIV compared to Fluzone QIV during a 2 day follow up period to assess for an effect of the higher antigen content, and the results showed that the relative risk of fever was 0.97 (overall/subject, 3.6% for Flulaval QIV vs. 3.7% for Fluzone QIV). No febrile seizures were reported in proximity to vaccination.

Fluarix and Fluarix Quadrivalent were approved for use in individuals 6 months of age and older in January 2017 (reviewed in STN 125127/834) for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. The volume of a single dose for persons 6 months of age and older is 0.5 mL; each dose contains 15 µg HA of each influenza viral strain. The pivotal study to support

licensure in infants and children 6 to < 36 months of age was a clinical disease endpoint efficacy study with non-influenza comparators.

Afluria and Afluria Quadrivalent were approved for use in individuals 6 months of age and older in October 2018 (reviewed in STN 125254/692) for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. The dosing regimen for infants 6 to < 36 months of age is single dose volume of 0.25 mL containing 7.5 µg HA of each influenza viral strain compared with 15 µg HA per strain in a 0.5 mL single dose volume indicated for persons 3 years of age and older. Fluzone Quadrivalent was the active comparator for the pivotal study to support licensure in infants and children 6 to < 36 months of age, and the dosing regimen reflects the currently licensed dosing regimen for Fluzone Quadrivalent.

Although each of the studies for the currently approved inactivated split-virus influenza vaccines include a single dose volume of 0.5 mL, they were independently conducted and are comprised of differing study designs, which does not allow for direct comparison of similar results between studies. The approval of each of the currently approved inactivated split-virus influenza vaccines at a single dose volume of 0.5 mL for children 6 to < 36 months of age reflects that the higher antigen content has been well tolerated in this young age group.

A live, cold-adapted, attenuated influenza virus vaccine is currently indicated for use in persons 2 through 49 years of age. The efficacy of FluMist has been demonstrated in clinical studies of children; however, the use of FluMist in children is limited by the increased risk of wheezing in very young children.

The most frequent adverse events after seasonal inactivated influenza vaccination are local adverse reactions, resulting in pain, erythema and induration in up to 65% of individuals. Serious adverse events associated with influenza vaccination are uncommon. Anaphylaxis has been reported after influenza vaccination but occurs rarely (0-10 per million doses of vaccine (12). Increased rates of Guillain-Barré syndrome (GBS) were reported during the swine influenza virus vaccination campaign of 1976. Observational studies since then have identified an increased risk of at most 1 additional GBS case per million vaccinated persons associated with seasonal influenza vaccines. Influenza vaccination has also been associated in passive surveillance studies with an increased rate of febrile seizures in children, potentially related to co-administration with pneumococcal conjugate vaccine (Prevnar13) (13).

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

Fluzone Quadrivalent was approved by the FDA in June 2013 for use in persons 6 months of age and older. Formulations of Fluzone have been licensed in the US since 1947 as a whole-virus preparation, and since 1980 as a split-virus preparation. Numerous prospective clinical trials and observational studies in the past two decades have demonstrated Fluzone vaccine's safety, immunogenicity and effectiveness.

Sanofi Pasteur has introduced two additional formulations of its trivalent Fluzone vaccine, both manufactured using processes similar to Fluzone (and (b) (4) Fluzone Quadrivalent). Fluzone High-Dose contains 60 µg of HA per strain (180 µg total for trivalent formulation per 0.5 mL dose) and is approved for use in persons 65 years of age and older. Fluzone Intradermal is formulated for intradermal administration and

contains 9 µg of HA per strain (27 µg total per 0.1 mL dose for the trivalent formulation). Fluzone Intradermal is approved for use in persons 19 through 64 years of age.

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

The initial submission of the GRC88 clinical protocol to IND 14078 was in February 2015, and the applicant submitted a request for comment and advice with the protocol submission regarding whether the proposed study design would support approval of a universal single dose volume of 0.5 mL for individuals 6 months and older. After several communications, the final version of the protocol incorporated our requests to assess safety and immunogenicity with hypothesis driven outcomes rather than descriptive outcomes. The applicant revised the primary endpoint to assess non-inferiority of fever rates between treatment arms and increased the sample size to adequately power the study accordingly. In addition, immunogenicity was assessed in terms of geometric mean titer (GMT) ratios and seroconversion rates (SCR) with pre-specified non-inferiority success criteria as secondary endpoints.

Refer to Section 2.3 regarding the considerations about differences in dose volume and antigen content for subjects 6 to < 36 months of age that informed our request for the non-inferiority of fever rates between treatment arms to be the primary endpoint.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

This submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

According to the applicant, all studies submitted in this supplement, with the exceptions listed below, were conducted in accordance with Good Clinical Practice, the Declaration of Helsinki, International Conference on Harmonization guidelines, and applicable national and local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

In Section 3.5.8 of the GRC88 Clinical Study Report, the applicant identified one site (009) in which a for-cause audit was conducted. Enrollment at Site 009 was stopped at 31 subjects due to multiple irregularities detected at the first monitoring visit. Irregularities included inadequate source documentation, failure to fully complete informed consent forms, pre-filled diary cards for visits not yet occurring and data entered into the electronic data system with no source available to verify the data. The issues were identified as “safety data integrity issues,” and analysis of safety data was conducted with and without data from Site 009. Results for the primary and secondary endpoints were similar when data from Site 009 were excluded.

CBER Bioresearch Monitoring (BIMO) inspections were issued at four clinical study sites that participated in the conduct of the Study GRC88. The inspection of Site 019 revealed that the vaccine storage equipment experienced a temperature excursion outside the recommended range for storing the vials of the inactivated influenza vaccine (IIV) which affected 26 subjects. An information request (IR) was sent to the applicant on October

10, 2018, to address these findings. The applicant adequately addressed the IR in an amendment submitted to the supplement on November 30, 2018, identifying two additional sites (016 [n=59] and 021 [n=7]) that experienced similar vaccine storage temperature excursions outside the recommended range for storage of IIV with additional analyses of primary and secondary endpoints excluding subjects affected by the vaccine temperature storage excursion. Overall, the inspections did not reveal significant problems that impacted the outcomes of the primary or secondary endpoints submitted in this application. Please refer to the BIMO review memo dated 11 December 2018 for the full review.

3.3 Financial Disclosures

In accordance with 21 CFR 54, Sanofi Pasteur submitted FDA Form 3454 with this supplement, certifying that the applicant had not entered into any financial arrangement with any clinical investigators involved in the trials comprising this licensure application, whereby the value of compensation to the investigator could be affected by the outcome of the study, as defined in 21 CFR 54.2(a). The applicant also certifies that each listed clinical investigator required to disclose to the applicant whether the investigator had a proprietary interest in this product or a significant equity in the applicant as defined in 21 CFR 54.2(b) did not disclose any such interests. The applicant further certifies that no investigators were the recipients of significant payments as defined in 21 CFR 54.2(f).

Table 1. Financial Disclosures for Study GRC88 (NCT 02915302)

Covered clinical study (name and/or number): Study GRC88 (NCT 02915302)		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 266 investigators at 38 US sites		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

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

4.2 Assay Validation

The bioassay reviewer verified that the hemagglutination inhibition (HAI) titers used to measure the immunogenicity secondary endpoints for this study were validated. For full review of the applicant's assay information, please refer to the review memo from the Office of Biostatistics dated 15 January 2019.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Vaccine-mediated protection against influenza likely involves both humoral and cellular immunity. Influenza vaccines elicit antibodies that inhibit influenza virus hemagglutination of red blood cells *in vitro*. Post-vaccination hemagglutination inhibition (HAI) antibody titers have been used to support regulatory approval of influenza

vaccines, though specific levels of antibody have not been absolutely correlated with protection from influenza illness. In some studies, HAI antibody titers of ≥ 1:40 have been associated with protection from influenza illness in up to 50% of subjects (14, 15).

4.5 Statistical

The statistical reviewer verified that the primary and secondary study endpoint analyses cited by the applicant were supported by the submitted data. For full details of the statistical review please refer to the review memo from the Office of Biostatistics and Epidemiology dated 20 December 2018.

4.6 Pharmacovigilance

No changes were recommended to the routine pharmacovigilance plan proposed for Fluzone Quadrivalent. No postmarketing safety studies or risk evaluation and mitigation strategies (REMS) were recommended. For full review of the Applicant's pharmacovigilance plan please refer to the review memo from the Office of Biostatistics and Epidemiology dated 10 December 2018.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

A single phase 4 Study, GRC88, was submitted to this BLA to serve as the primary basis for licensure and is described in detail in Section 6.1.

The following sections were deleted from this review as they were not applicable to this application: 4.1: Chemistry, Manufacturing, and Controls, 4.3: Nonclinical Pharmacology/Toxicology, 4.4.2: Human Pharmacodynamics, 4.4.3: Human Pharmacokinetics, 6.1.5: Directions for Use, 6.1.12.5: Adverse Events of Special Interest, 7: Integrated Overview of Efficacy and 8: Integrated Overview of Safety.

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

The following files served as the basis for the clinical review of STN 103914/6208:

STN 103914/6208.0 modules:

- 1.3.4 Financial Disclosures
- 1.6.3 Correspondence Regarding Meetings
- 1.9.1 Pediatric Waiver Request
- 1.14 Labeling
- 2.5 Clinical Overview
- 2.7 Clinical Summaries
- 5 Clinical Study Reports
- Amendments 5001 through 5007 were reviewed for materials relevant to the clinical review process.

5.3 Table of Studies/Clinical Trials

Table 2. Clinical Study included in Supplemental BLA for Fluzone Quadrivalent

Study Number; Population; Country; Start/End Dates	Study Description	Primary Objective	Test Products; Dosage regimen	Number of Subjects
GRC88 Healthy children 6 to < 36 months of age United States 23 Sept 2016/ 6 March 2017	Phase 4, randomized, observer-blind, 2 arm, multi-center study	To compare the rate of any fever (temperature ≥ 100.4°F [38.0°C]) following the 0.5 mL dose(s) of Fluzone QIV to that following the 0.25 mL dose(s) of Fluzone QIV during the 7 days after either vaccination (Dose 1 and Dose 2 combined)	Visit 1: 1 dose of Fluzone QIV Group 1: 0.25 mL Group 2: 0.5 mL Visit 2[a]: 1 dose of Fluzone QIV Group 1: 0.25 mL Group 2: 0.5 mL	Total Randomized: Group 1: 955 Group 2: 995 Safety Analysis Set: Group 1: 949 Group 2: 992 PP Analysis Set: Group 1: 502 Group 2: 525

Source: Adapted from STN 103914/6208: module 2.5 Clinical Overview
[a] For subjects requiring 2 doses of influenza vaccine, as per Advisory Committee on Immunization Practices guidance, a second dose of the assigned vaccine dose was administered at Visit 2 (28 [window, 28–35] days after Visit 1).

5.4 Consultations

5.4.1 Advisory Committee Meeting

Multidisciplinary review of the data submitted for this supplement did not reveal new issues about the product that required the opinion of an independent panel of experts, including the Vaccines and Related Biological Products Advisory Committee (VRBPAC). Previous VRBPAC meetings have discussed the need for a quadrivalent influenza vaccine.

5.5 Literature Reviewed

1. WHO Fact Sheet November 2018. At http://www.who.int/mediacentre/factsheets/fs211/en/
2. Schanzer D, Langley J, Tam T. Hospitalization Attributable to Influenza and Other Viral Respiratory Illnesses in Canadian Children. Pediatr Infect Dis J 2006;25:795-800.
3. CDC (Centers for Disease Control and Prevention). Influenza vaccination coverage among children aged 6-23 months--United States, 2005-06 influenza season. MMWR 2007;56(37):959-63.
4. Poehling KA, Edwards KM, Weinberg GA, Szilagyi P et al, for the New Vaccine Surveillance Network. The under-recognized burden of influenza in young children. NEJM 2006;355:31-40.

5. Brownstein JS, Mandl KD. Pediatric population size is associated with local timing and rate of influenza and other acute respiratory infections among adults. Ann Emerg Med 2008;52:63-8.
6. Barr IG, McCauley J, Cox N et al. Writing Committee of the World Health Organization Consultation on Northern Hemisphere Influenza Vaccine Composition for 2009–2010. Epidemiological, antigenic and genetic characteristics of seasonal influenza A (H1N1), A (H3N2) and B influenza viruses: Basis for the WHO recommendation on the composition of influenza vaccines for use in the 2009-2010 Northern Hemisphere season. Vaccine 2010;28(5) :1156-67. Online version of manuscript accessed for Table (Dec 2009).
7. Ambrose CS, Levin MJ. The rationale for quadrivalent influenza vaccines. Hum Vaccin Immunother. 2012;8(1):81–8.
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9. Hobson D, Curry RL, Beare AS, Ward-Gardner A. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. J Hyg Camb 1972; 70:767-777.
10. Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, Cox NJ, Fukuda K. Influenza-associated hospitalizations in the United States. JAMA. Sep 15, 2004; 292(11):1333-40
11. Halasa NB, Gerber MA, Berry AA, et al. Safety and immunogenicity of full-dose trivalent inactivated influenza vaccine (TIV) compared with half-dose TIV administered to children 6 through 35 months of age. J Pediatr Infect Dis Soc. 2015;4(3):214-24.
12. Reed C, Meltzer MI, Finelli L, Fiore A. Public health impact of including two lineages of influenza B in a quadrivalent seasonal influenza vaccine. Vaccine. 2012 Mar 2;30(11):1993-8.
13. Talbot HK, Griffin MR, Chen Q, Zhu Y, Williams JV, Edwards KM. Effectiveness of seasonal vaccine in preventing confirmed influenza-associated hospitalizations in community dwelling older adults. J Infect Dis. 2011 Feb 15;203(4):500-8.
14. Reber A, Immunological assessment of influenza vaccines and immune correlates of protection. Expert Rev Vaccines 12 (5):519-36 (2013).
15. Ohmit SE, Petrie JG, Cross RT, Johnson E, Monto AS. Influenza hemagglutination inhibition antibody titer as a correlate of vaccine-induced protection*. J. Infect. Dis.* 204(12): 1879–85 (2011).

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Study GRC88

Title: Safety and Immunogenicity of Fluzone® Quadrivalent Vaccine Administered to Healthy Children 6 to < 36 Months of Age

The first subject was enrolled in the study on 23 September 2016, and the study was completed on 6 March 2017. The data lock point (date of database freeze) was on 25 July 2017.

6.1.1 Objectives

The purpose of this study was to describe the safety and immunogenicity of the 0.5 mL dose as compared to the 0.25 mL dose of Fluzone Quadrivalent vaccine in children 6 to < 36 months of age with the intent to modify the vaccine's prescribing information to specify that the 0.5 mL dose is indicated for all ages 6 months and older. The primary and secondary objectives are listed below.

Primary Objective: To compare the rate of any fever (temperature ≥ 100.4°F [38.0°C]) following the 0.5 mL dose of Fluzone Quadrivalent vaccine to that following the 0.25 mL dose of Fluzone Quadrivalent vaccine during the 7 days after either vaccination (Dose 1 and Dose 2 combined) in subjects 6 to < 36 months of age.

Secondary Objective: To compare antibody responses induced by the 0.5 mL dose of Fluzone Quadrivalent vaccine to those induced by the 0.25 mL dose of Fluzone Quadrivalent vaccine as assessed by geometric mean titer (GMT) ratios and seroconversion (SC) rate differences after the final vaccination in subjects 6 to < 36 months of age.

6.1.2 Design Overview

Study GRC88 was a Phase IV, randomized, observer-blind, 2-arm, multi-center study to evaluate the safety and immunogenicity of 2 different dose levels of Fluzone Quadrivalent influenza vaccine (QIV) in healthy children 6 to < 36 months of age. Subjects were randomized 1:1 to receive either 0.25 mL of Fluzone QIV or 0.5 mL of Fluzone QIV. Enrollment was stratified by age at each site so that approximately 50% of subjects were 6 to <24 months of age and approximately 50% were 24 to <36 months of age. A total of 1950 subjects were enrolled. The study duration was 56-91 days, depending on number of vaccine doses administered.

Subjects received 1 intramuscular (IM) injection of Fluzone QIV (0.25 mL [Group 1] or 0.5 mL [Group 2]) at Visit 1. For subjects for whom 2 doses of influenza vaccine were recommended per ACIP guidance, a second IM injection (same dose administered at Visit 1) was administered at Visit 2, 28-35 days after Visit 1. Subjects were followed for collection of safety data for 28 days following the last vaccination received.

A subset of subjects (approximately 75% of the total subjects in each treatment arm) had 2 blood samples collected: one sample at Visit 1 prior to vaccination and the second at Visit 2 for subjects only requiring one dose of vaccine or at Visit 3 (28-35 days after Visit 2) for subjects requiring two doses of vaccine per ACIP recommendations.

The collection of safety data included any immediate Adverse Reactions (ARs) within 20 minutes of vaccine administration, solicited local and systemic adverse reactions from Day 0-7, and unsolicited adverse events (AEs) and serious adverse events (SAEs) from Visit 1-2 for subjects receiving one dose of vaccine and from Visit 1-3 for subjects receiving two doses of vaccine. There was no safety follow up beyond Visit 2 (for subjects receiving 1 dose) or Visit 3 (for subjects receiving 2 doses).

6.1.3 Population

All healthy children 6 to <36 months of age were eligible.

A potential subject had to meet all of the following criteria to be considered for study enrollment:

1) Subjects had to be 6 to < 36 months of age on the day of first study vaccination (study product administration).
2) Born at full term of pregnancy (≥ 37 weeks) and/or with a birth weight ≥ 2.5 kg. Note: This inclusion criterion only applies to subjects 6 to < 12 months of age on the day of the first study visit.
3) Informed consent form has been signed and dated by the parent(s) or guardian(s).
4) Subject and parent/guardian are able to attend all scheduled visits and to comply with all trial procedures.

Exclusion Criteria:

1) Participation at the time of study enrollment (or in the 30 days preceding the first trial vaccination) or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure. Note: Subjects may be considered eligible for enrollment if no intervention for the other study occurred within the 30 days prior to the first study vaccination and none are planned before the subject would complete safety surveillance for the present study.
2) Receipt of any vaccine in the 30 days preceding the first trial vaccination, or planned receipt of any vaccine before Visit 2 for subjects receiving 1 dose of influenza vaccine or Visit 3 for subjects receiving 2 doses of influenza vaccine.
3) Previous vaccination against influenza (in the 2016–2017 season) with either the trial vaccine or another vaccine.
4) Receipt of immune globulins, blood, or blood-derived products in the past 3 months.
5) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months).
6) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccine used in the trial or to a vaccine containing any of the same substances.
7) Thrombocytopenia, which may be a contraindication for intramuscular vaccination, at the discretion of the Investigator.
8) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination.
9) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily.
10) Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion. Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, autoimmune disorders, diabetes, psychomotor diseases, and known congenital or genetic diseases
11) Moderate or severe acute illness/infection (according to Investigator judgment) on the day of planned vaccination or febrile illness (temperature ≥ 100.4°F [38.0°C]). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.
12) Identified as a natural or adopted child of either the Investigator or an employee with direct involvement in the proposed study.

13) History of serious Adverse Reactions to any influenza vaccine.
14) Personal history of Guillain-Barré syndrome (GBS).
15) Any condition that in the opinion of the Investigator would pose a health risk to the subject if enrolled or could interfere with the evaluation of the vaccine.
16) Personal history of clinically significant developmental delay (at the discretion of the Investigator), neurologic disorder, or seizure disorder.
17) Known seropositivity for human immunodeficiency virus, hepatitis B, or hepatitis C.

Reviewer Comment: The inclusion and exclusion criteria were appropriate for this study and allow for generalizability to a healthy pediatric population under 3 years of age.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects were administered one of the following vaccines:

- Fluzone Quadrivalent vaccine, No Preservative: Pediatric Dose (0.25 mL dose), 2016–2017 formulation. Batch number UT5583JA (expiration date 30 June 2017) was used in this study.
- Fluzone Quadrivalent vaccine, No Preservative (0.5 mL dose), 2016–2017 formulation. Batch number UI629AA (expiration date 30 June 2017) was used in this study.

One or two doses were administered according to Advisory Committee on Immunization Practices recommendations. If two doses were recommended, a second dose of the same volume as the first dose was administered approximately 28 days after the first dose.

Each 0.25 mL and 0.5 mL dose of vaccine contains 7.5 µg and 15 µg HA, respectively, of each antigen:

- A/California/07/2009 X-179A (H1N1)
- A/Hong Kong/4801/2014 X-263B (H3N2)
- B/Brisbane/60/2008 (Victoria lineage; B1)
- B/Phuket/3073/2013 (Yamagata lineage; B2)

The product was provided in 0.25 mL or 0.5 mL, pre-filled, single-dose syringes. The vaccine was administered intramuscularly into the anterolateral muscle of the thigh or the deltoid muscle, as appropriate for age.

6.1.6 Sites and Centers

Study GRC88 was conducted at 38 centers in the United States.

6.1.7 Surveillance/Monitoring

Monitoring procedures for Study GRC88 are described in Table 3 below.

Table 3. Study GRC88. Study Procedures.

	All Subjects	All Subjects	Subjects receiving 1 dose	Subjects receiving 2 doses	Subjects receiving 2 doses	Subjects receiving 2 doses
Visit Number	**Visit 1**	**Telephone Contact**	**Visit 2**	**Visit 2**	**Telephone Contact**	**Visit 3**
Study Timelines	**Day 0**	**Visit 1 + 8 days**	**Visit 1 + 28 days**	**Visit 1 + 8 days**	**Visit 2 + 8 days**	**Visit 2 + 28 days**
Informed consent	X					
Inclusion/Exclusion criteria	X					
Demographic data	X					
Medical History	X					
Influenza vaccination history	X					
History directed physical exam	X			X		
Temperature	X			X		
Randomization	X					
Blood sample (BL)[a]	BL1		BL2			BL2
Vaccination[b,c]	X			X		
Immediate surveillance (20 minutes)	X			X		
Diary card (DC) provided	DC1			DC2		
Telephone contact		X			X	
Diary card reviewed and collected			DC1	DC1		DC2
Interim history			X	X		X
Termination record[e]			X			X
Serious adverse events	X	X	X	X	X	X

Source: STN 103914/6208; GRC88 Clinical Study Report, Table 3.1, p. 43-44.

[a] A blood sample, approximately 5 mL, was collected from subjects randomly assigned to the immunogenicity subset at Visit 1, prior to vaccination, and at either Visit 2 (for subjects receiving 1 influenza vaccine dose) or at Visit 3 (for subjects receiving 2 influenza vaccine doses).

[b] Group 1 was assigned to receive a 0.25 mL dose of Fluzone Quadrivalent vaccine at Day 0; Group 2 was assigned to receive a 0.5 mL dose of Fluzone Quadrivalent vaccine at Day 0.

[c] One or 2 doses of influenza vaccine were administered according to the Advisory Committee on Immunization Practices guidance in effect during the study. If 2 doses of influenza vaccine were indicated, 1 dose was administered during Visit 1 and the second dose (of the same volume as the first dose) was administered approximately 28 days later during Visit 2.

[d] The subject's parent/guardian was contacted by telephone on Day 8 after vaccination as a reminder to complete the diary card and to bring it with them to the next visit.

[e] The termination form was completed at Visit 2 for subjects receiving 1 dose of influenza vaccine or at Visit 3 for subjects receiving 2 doses of influenza vaccine.

The preferred route of temperature measurement in this study was rectal. In cases where rectal temperature could not be obtained, a non-preferred route (e.g., axillary) could be used. Parents/guardians were instructed that tympanic thermometers must not be used.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint: Rate of any fever (temperature ≥ 100.4°F [38.0°C]) during the 7 days after either vaccination (Dose 1 and Dose 2 combined) in each vaccine group. Non-inferiority was demonstrated if the upper bound of the 2-sided 95% confidence interval (CI) of the rate of difference between Group 2 (subjects receiving 0.5 mL of vaccine) and Group 1 (subjects receiving 0.25 mL of vaccine) was < 5%.

Secondary Endpoints:

- Geometric mean titers (GMTs): The hemagglutination inhibition (HAI) GMTs (for each of the 4 virus strains) at 28 (window, 28–35) days after the final vaccination. Non-inferiority for GMTs was demonstrated if the lower limit (LL) of the 2-sided 95% CI of the GMT ratio was > 0.67 for each of the 4 virus strains contained in the vaccine.
- Seroconversion (SC) rates: The percentages of subjects with either a pre-vaccination titer < 10 (1/dil) and a post-vaccination titer ≥ 40 (1/dil), or a pre-vaccination titer ≥ 10 (1/dil) and a ≥ 4-fold increase in post-vaccination titer at 28 (window, 28–35) days after the final vaccination. Non-inferiority for SC rates was demonstrated if the LL of the 2-sided 95% CI was > -10% for each of the 4 strains contained in the vaccine.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Assuming a total planned enrollment sample size of approximately 2190 (approximately 1095 subjects would be randomly assigned to receive the 0.5 mL dose of vaccine, and approximately 1095 would be subjects randomly assigned to receive the 0.25 mL dose of vaccine):

- Considering an attrition rate of 5% for the Safety Analysis Set, a 1-sided alpha of 2.5%, an expected 14.3% rate of fever (from Study QIV04) for each vaccine dosing group and a margin of 5%, non-inferiority for fever would be demonstrated with a power of approximately 90%.
- Considering 1600 subjects were to be randomly assigned to the immunogenicity subset, an attrition rate of 20% for the PP Analysis Set, and a 1-sided alpha of 2.5% for each test, the power to demonstrate non-inferiority for both GMTs and SC rates was to be approximately 91%.

Assuming the same GMTs for each vaccine dosing group, a standard deviation of log titers against each strain of 0.7 and a non-inferiority margin of 0.67, non-inferiority for GMTs would be demonstrated with a power of approximately 97.6%.
Assuming for each strain the same expected SC rates for each vaccine dosing group (90.9%, 95.4%, 72%, and 57.5% for strains A/H1N1, A/H3N2, B1, and B2, respectively, based on Study QIV04) and a non-inferiority margin of 10% for each strain, non-inferiority for SC rates would be demonstrated with a power of approximately 93.2%.

Please refer to the Statistical Review for more details of the statistical considerations and the statistical analysis plan.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The Safety Analysis Set was defined as those subjects who received study vaccine. All subjects had their safety analyzed after any dose according to the dose of vaccine they actually first received. Safety data recorded for a vaccine received out of the protocol design were to be excluded from the analysis (and listed separately). Safety analysis after each dose was assessed in the subset of the Safety Analysis Set having received that dose.

There were 2 analysis populations used in the analysis of immunogenicity in Study GRC88: the Full Analysis Set (FAS) and the Per-Protocol (PP) Analysis Set.

1) The FAS was defined as subjects randomly assigned to the immunogenicity subset who received at least 1 dose of the study vaccine and had a valid post-vaccination serology result for at least 1 strain.
2) The PP Analysis Set was a subset of the FAS. Subjects who presented with at least 1 of the following relevant protocol deviations were excluded from the PP Analysis Set:
    - Subject did not meet all protocol-specified inclusion criteria or met at least 1 of the protocol specified exclusion criteria.
    - Subject did not complete the vaccination schedule as per protocol.
    - Subject received a vaccine dose other than the one that he/she was randomly assigned to receive.
    - Preparation and/or administration of vaccine was not done as per protocol.
    - For subjects receiving 2 doses of vaccine, subject did not receive the second dose within the proper time window (28–35 days after the first vaccination).
    - Subject did not provide a post-dose serology sample in the proper time window (28–35 days) after the final vaccination or a post-dose serology sample was not drawn.
    - Subject received a protocol-prohibited therapy/medication/vaccine that might impact antibody response to the study vaccine.
    - Subject's post-vaccination serology sample did not produce a valid HAI test result for any strain.
    - Any other deviation identified during conduct of the study and judged by the clinical team during data review as having a potential impact on the assessment of immunogenicity.
    - Re-randomization of a subject.
    - Inclusion in the immunogenicity subset after not being assigned to the subset originally.
    - Receipt of study vaccine not corresponding to the medication (vaccine) ID assigned to the subject.

    *For clarification, three sites were identified to have problems with a 'temperature excursion of the vaccine storage equipment' [sites 016 (n=59), 019 (n=26), and 021 (n=7)], and affected subjects from these three sites were excluded from the secondary immunogenicity analyses because this was considered a protocol violation. Refer to Section 3.2 for additional details.

6.1.10.1.1 Demographics

The demographics for the safety analysis set are displayed in Table 4 below.

Table 4. Study GRC88. Subject Demographics (Safety Analysis Set)

	Group 1 (N=949)	Group 2 (N=992)	Total (N=1941)
Sex: n (%) Male	480 (50.6)	497 (50.1)	977 (50.3)
Sex: n (%) Female	469 (49.4)	495 (49.9)	964 (49.7)
Age (months) Mean (SD)	20.4 (8.75)	20.5 (8.55)	20.5 (8.65)
Age (months) Min; Max	6; 35	6; 36	6; 36
Age (months) Median	21	21	21
Racial Origin: n (%) White	717 (75.6)	725 (73.1)	1442 (74.3)
Racial Origin: n (%) Asian	1 (0.1)	8 (0.8)	9 (0.5)
Racial Origin: n (%) Black or African-American	178 (18.8)	195 (19.7)	373 (19.2)
Racial Origin: n (%) American Indian or Alaska Native	9 (0.9)	10 (1.0)	19 (1.0)
Racial Origin: n (%) Native Hawaiian or Pacific Islander	4 (0.4)	5 (0.5)	9 (0.5)
Racial Origin: n (%) Mixed Origin	36 (3.8)	43 (4.3)	79 (4.1)
Racial Origin: n (%) Missing	4 (0.4)	6 (0.6)	10 (0.5)
Ethnicity: n (%) Hispanic or Latino	206 (21.7)	221 (22.3)	427 (22.0)
Ethnicity: n (%) Not Hispanic or Latino	731 (77.0)	763 (76.9)	1494 (77.0)
Ethnicity: n (%) Missing	12 (1.3)	8 (0.8)	20 (1.0)

Source: Adapted from STN 103914/6208; GRC88 Clinical Study Report, Table 4.5, p. 86.
N: number of subjects analyzed according to the Safety Analysis Set and fulfilling column header
n: number of subjects fulfilling the item listed
M: number of subjects with available data for the relevant endpoint
SD: standard deviation
Min: minimum; Max: maximum
Group 1: Subjects who received 0.25 mL dose(s) of Fluzone Quadrivalent vaccine
Group 2: Subjects who received 0.5 mL dose(s) of Fluzone Quadrivalent vaccine

> ***Reviewer Comment: The subject demographics are balanced between treatment groups with respect to gender, age, racial origin, and ethnicity. The majority of subjects were White and not Hispanic or Latino***.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Subjects enrolled in this study were healthy children.

6.1.10.1.3 Subject Disposition

Table 5. Study GRC88. Subject Disposition.

	Group 1 (N=955) n (%)	Group 2 (N=995) n (%)	All (N=1950) n (%)
All randomized subjects	955 (100.0)	995 (100.0)	1950 (100.0)
Randomized but did not receive vaccine	6 (0.6)	3 (0.3)	9 (0.5)
All subjects randomly assigned to the immunogenicity subset	715 (74.9)	745 (74.9)	1460 (74.9)
Safety Analysis Set[a]	949 (99.4)	992 (99.7)	1941 (99.5)
Received 1 dose of vaccine	442 (46.3)	475 (47.7)	917 (47.0)
Received 2 doses of vaccine	507 (53.1)	517 (52.0)	1024 (52.5)
Completed trial	890 (93.2)	917 (92.2)	1807 (92.7)
Early Termination	65 (6.8)	78 (7.8)	143 (7.3)
Serious adverse event	1 (0.1)	0 (0)	1 (<0.1)
Other adverse event (AE)	2 (0.2)	0 (0)	2 (0.1)
Noncompliance with the protocol	20 (2.1)	27 (2.7)	47 (2.4)
Lost to follow-up	19 (2)	29 (2.9)	54 (2.8)
Voluntary withdrawal not due to an AE	22 (2.3)	29 (2.9)	51 (2.6)

Source: Adapted from STN 103914/6208: GRC88 Clinical Study Report, Table 4.1, p. 78 and Table 9.10, p. 143.
N: number of randomized subjects fulfilling column header
n: number of subjects satisfying the criteria listed in the first column
Group 1: Subjects randomly assigned to receive 0.25 mL dose(s) of Fluzone Quadrivalent vaccine
Group 2: Subjects randomly assigned to receive 0.5 mL dose(s) of Fluzone Quadrivalent vaccine
[a] Safety Analysis Set is defined as those subjects who received at least 1 dose of study vaccine

Reviewer Comment: The subject disposition is generally balanced between treatment groups. The percentage of subjects who discontinued is consistent with percentages seen in similar trials (<10%). A small percentage of subjects discontinued due to an adverse event.

6.1.11 Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary objective of this study was to compare the rate of any fever (temperature ≥ 100.4°F [38.0°C]) following the 0.5 mL dose(s) of Fluzone Quadrivalent vaccine (Group 2) to that following the 0.25 mL dose(s) of Fluzone Quadrivalent vaccine (Group 1) during the 7 days after either vaccination (Dose 1 and Dose 2 combined) in subjects 6 to < 36 months of age. Non-inferiority was demonstrated if the upper bound of the 2-sided 95% CI of the rate difference between Group 2 and Group 1 was < 5%.

For Dose 1 and Dose 2 combined, the fever rate of Group 2 (12.15%) was not statistically significantly higher than the fever rate of Group 1 (11.31%) based on the pre-

specified criterion for non-inferiority; the difference in fever rates between the groups was 0.84% (95% CI: -2.13%; 3.8%). See Table 6 below.

Table 6. Study GRC88. Non-Inferiority Comparison of 2 Dose Levels of Fluzone Quadrivalent Vaccine (0.5 mL vs 0.25 mL) as Assessed by the Difference in Fever Rates– Safety Analysis Set.

	Group 1 (N=949) n/M	Group 1 (N=949) Fever rate[a]	Group 2 (N=992) n/M	Group 2 (N=992) Fever rate[a]	Differences in Fever rates[b] (95% CI)	Non-inferiority[c]
Fever Rate	101/893	11.31	113/930	12.15	0.84 (-2.13; **3.8**)	Yes

Source: Adapted from sBLA 103914\6208: GRC88 Clinical Study Report: Table 9.25, p. 165
n: number of subjects who experienced fever within the solicited period
M: number of subjects with temperature data during the 7 days after vaccination
Group 1: Subjects who received 0.25 mL dose(s) of Fluzone Quadrivalent vaccine
Group 2: Subjects who received 0.5 mL dose(s) of Fluzone Quadrivalent vaccine
[a] Fever is defined as body temperature of >= 100.4 F
[b] Difference in fever rate = fever rate in Group 2 minus fever rate in Group 1
[c] Non-inferiority demonstrated if the upper limit of the 2-sided 95% CI of the difference in fever rates between groups was < 5%

> ***Reviewer Comment: Because the primary endpoint based on the safety analysis set was pre-specified, inclusion of all subjects who received at least 1 dose of vaccine is the appropriate analysis set (safety analysis set) to use to evaluate the primary endpoint.***

An additional analysis of the primary endpoint was conducted excluding subjects who received vaccines affected by vaccine temperature excursions at 3 sites (016, 019, and 021) and all subjects from site 009, where there was a safety data integrity concern. The success criterion for non-inferiority of fever rates between the treatment groups was met in this re-analysis. See Table 7 below.

Table 7. Study GRC88. Non-Inferiority Comparison of 2 Dose Levels of Fluzone Quadrivalent Vaccine (0.5 mL vs 0.25 mL) as Assessed by the Difference in Fever Rates (Excluding subjects from sites 016, 019 and 021 who received vaccine with a potential temperature excursion and all subjects from site 009) – Safety Analysis Set.

	Group 1 (N=886) n/M	Group 1 (N=886) Fever rate[a]	Group 2 (N=932) n/M	Group 2 (N=932) Fever rate[a]	Differences in Fever rates[b] (95% CI)	Non-inferiority[c]
Fever Rate	99/837	11.8	110/874	12.6	0.8 (-2.4; **3.9**)	Yes

Source: Statistical Reviewer-generated. Refer to the Statistical Review and Evaluation of sBLA 103914/6208, Table 2.
n: number of subjects who experienced fever within the solicited period
M: number of subjects with temperature data during the 7 days after vaccination
Group 1: Subjects who received 0.25 mL dose(s) of Fluzone Quadrivalent vaccine
Group 2: Subjects who received 0.5 mL dose(s) of Fluzone Quadrivalent vaccine
[a] Fever is defined as body temperature of >= 100.4 F

[b] Difference in fever rate = fever rate in Group 2 minus fever rate in Group 1
[c] Non-inferiority demonstrated if the upper limit of the 2-sided 95% CI of the difference in fever rates between groups was < 5%

Reviewer Comment: A re-analysis of the primary endpoint excluding data where there was a protocol violation or where there were data integrity concerns indicated that the study still met non-inferiority success criteria, so the study outcome was not affected by the concerns identified.

The sponsor did not provide data to support vaccine storage at alternative temperatures and even though the outcomes are similar, the data submitted to this BLA do not support vaccine storage at alternative temperatures.

6.1.11.2 Analyses of Secondary Endpoints

The secondary objective of this study was to compare antibody responses induced by the 0.5 mL dose of Fluzone Quadrivalent vaccine to those induced by the 0.25 mL dose of Fluzone Quadrivalent vaccine as assessed by the ratio of GMTs and SC rate differences after the final vaccination in subjects 6 to < 36 months of age.

Geometric Mean Titers:

For each comparison, non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the GMT ratio ($GMT_{0.5mL}$ divided by $GMT_{0.25mL}$) was > 0.67 for each of the 4 virus strains. See Table 7 below for results.

Table 7. Study GRC88. Non-Inferiority Comparison of 2 Dose Levels of Fluzone Quadrivalent Vaccine as Assessed by the Ratio of Geometric Mean Titers (GMTs)– Per Protocol Set.

Antigen Strain	Group 1 (N=502) M	Group 1 (N=502) GMT	Group 2 (N=525) M	Group 2 (N=525) GMT	Ratio of GMTs[a] (95% CI)	Non-inferiority[b]
A/H1N1	497	219	521	312	1.45 (**1.16**; 1.74)	Yes
A/H3N2	502	222	524	329	1.50 (**1.21**; 1.82)	Yes
B Victoria	497	262	521	348	1.33 (**1.09**; 1.62)	Yes
B Yamagata	501	247	525	349	1.41 (**1.17**; 1.70)	Yes

Source: sBLA 103914\6208.5005: Conducted Analyses on Immunogenicity Endpoints, Table 9.5, p. 5.
N: number of subjects analyzed according to the Per-Protocol Analysis Set and fulfilling column header
M: number of subjects with available data for the considered endpoint
CI: confidence interval
Group 1: Subjects who received 0.25 mL dose(s) of Fluzone Quadrivalent vaccine
Group 2: Subjects who received 0.5 mL dose(s) of Fluzone Quadrivalent vaccine
[a] Ratio of GMTs = GMT Group 2 divided by GMT Group 1
[b] Non-inferiority demonstrated if the lower limit of the 2-sided 95% CI of the ratio of GMTs between groups was > 0.67 (considered separately for each strain)

Seroconversion Rates:

For each comparison, non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference in SC rates (SC rate $_{0.5mL}$ minus SC rate $_{0.25mL}$) was > -10% for each of the 4 virus strains. See Table 8 below for results.

Table 8. Study GRC88. Non-Inferiority Comparison of 2 Dose Levels of Fluzone Quadrivalent Vaccine as Assessed by Difference in Seroconversion (SC) Rates– Per Protocol Set.

Antigen Strain	Group 1 (N=502) n/M	Group 1 (N=502) SC rate[a] %	Group 2 (N=525) n/M	Group 2 (N=525) SC rate[a] %	Difference in SC rates[b] (95% CI)	Non-inferiority[c]
A/H1N1	357/450	79.3	392/467	83.9	4.6 (**0.407**; 8.62)	Yes
A/H3N2	371/455	81.5	408/471	86.6	5.1 (**0.370**; 9.81)	Yes
B Victoria	393/450	87.3	414/467	88.7	1.3 (**-2.91**; 5.57)	Yes
B Yamagata	402/454	88.5	430/472	91.1	2.6 (**-1.36**; 6.51)	Yes

Source: sBLA 103914\6208.5005: Conducted Analyses on Immunogenicity Endpoints, Table 9.9, p. 9.
n: number of subjects analyzed according to the Per-Protocol Analysis Set and fulfilling column header
M: number of subjects with a valid serology result for the particular antigen, including results reported as < LLOQ or > ULOQ
LLOQ: lower limit of quantification; ULOQ: upper limit of quantification
CI: confidence interval
Group 1: Subjects who received 0.25 mL dose(s) of Fluzone Quadrivalent vaccine
Group 2: Subjects who received 0.5 mL dose(s) of Fluzone Quadrivalent vaccine
[a] SC (seroconversion) is defined as either a pre-vaccination hemagglutination inhibition titer < 1:10 and a post-vaccination titer >= 1:40 or a pre-vaccination titer >= 1:10 and at least a 4-fold increase in post-vaccination titer (considered separately for each strain)
[b] The difference in SC rates = SC rate of Group 2 minus SC rate of Group 1
[c] Non-inferiority demonstrated if the lower limit of the 2-sided 95% CI of the difference in SC rates was > -10% (considered separately for each strain)

> ***Reviewer Comment: The immunogenicity results demonstrated non-inferiority with slightly higher point estimates for GMTs and seroconversion rates with the 0.5 mL dose in Group 2 compared to the 0.25 mL dose in Group 1. Although the point estimate was slightly higher for the 0.5 mL dose volume, these data do not support superiority of the 0.5 mL dose compared to the 0.25 mL dose as there were no pre-specified criteria to demonstrate immunologic superiority of 0.5 mL volume compared to the 0.25 mL volume.***

6.1.11.3 Subpopulation Analyses

Analyses of Fever Rates by Age Group

A subgroup analysis by age showed that rates of fever between Group 1 and Group 2 were similar: among subjects 6 to < 24 months of age, rates were 12.05% and 15.66%, respectively; among subjects 24 to < 36 months of age, rates were 10.38% and 7.52%,

respectively. The younger age group did have higher rates of fever in general, and more grade 3 fevers, however these higher fever rates did not correlate with an increase in actions taken for the fever, such as medication use, contact with a health care provider, or hospitalization. See Table 9 below. Refer to Section 6.1.12.2 below for additional discussion and subgroup analyses of the fever rates by age subgroup.

> ***Reviewer Comment: Despite the higher fever rates seen in Group 2 vs. Group 1 in the younger age group, there were no associated increases in medication use, contact with a health care provider or hospitalization. Thus, the higher rates of fever did not correspond with a need for additional medical care and were not considered to be clinically significant enough to require medical attention. See Section 6.1.12.2 below for additional discussion and data.***

Analyses of Fever Rates by Gender

A subgroup analysis by gender showed that the fever rates between Group 1 and Group 2 were similar within the female subgroup (Group 1, 13.04% of subjects; Group 2, 13.45% of subjects; difference in fever rates = 0.41% (95% confidence interval [CI]: -4.07%; 4.85%) and male subgroup (Group 1, 9.65% of subjects; Group 2, 10.87% of subjects; difference in fever rates = 1.23% (95% CI: -2.73%; 5.17%). The point estimate of rates of fever trended higher in female subjects. See Table 9 below.

> ***Reviewer Comment: Higher point estimates for fever rates were seen in females. Limited conclusions can be drawn from this analysis since this is a post-hoc analysis, and the confidence intervals are overlapping.***

Analyses of Fever Rates by Race

A subgroup analysis by race separated treatment groups by white and non-white subgroups, given that the majority of the subject population was white. The fever rate differences between Group 1 and Group 2 were similar in the white subgroup (Group 1, 12.1% of subjects and Group 2, 11.9% of subjects), but differed between treatment groups for subjects in the non-white group, with fever rates trending higher in Group 2, (Group 1, 8.3% of subjects and Group 2 15.4% of subjects). See Table 9 below.

> ***Reviewer Comment: Because the majority of subjects identified themselves as white, the total subject numbers are notably different between the white and non-white subgroups. Limited conclusions can be drawn from this analysis since this is a post-hoc analysis and the number of subjects in the non-white subgroup was much lower than the number of subjects in the white subgroup.***

Table 9. Study GRC88. Comparison of Fever Rate of 2 Dose Levels of Fluzone Quadrivalent Vaccine by Age, Gender and Race – Safety Analysis Set.

	Subgroups	Group 1 n/M	Group 1 Fever Rate[a] % (95% CI)	Group 2 n/M	Group 2 Fever Rate % (95% CI)
Overall Fever Rate	6 to < 24 months	60/498	12 (9.3; 15.2)	83/530	15.7 (12.7; 19)
Overall Fever Rate	24 to < 36 months	41/395	10.4 (7.6; 13.8)	30/399	7.5 (5.1; 10.6)
Overall Fever Rate	Female	57/437	13 (10.; 16.6)	62/461	13.5 (10.5; 16.9)
Overall Fever Rate	Male	44/456	9.7 (7.1; 12.7)	51/469	10.9 (8.2; 14)
Overall Fever Rate	White	83/685	12.1 (9.8; 14.8)	83/694	11.9 (9.6; 14.6)
Overall Fever Rate	Non-white	14/169	8.3 (4.6; 13.5)	29/188	15.4 (10.6; 21.4)

Source: Adapted from: sBLA 103914\6208; Addendum to the GRC88 Clinical Study Report, Tables 9.12, 9.13, 9.14, 9.15 and Appendix 15, Tables 29 and 30.
n: number of subjects who experienced fever within the solicited period
M: number of subjects with valid temperature data during the 7 days after vaccination
Group 1: Subjects who received 0.25 mL dose(s) of Fluzone Quadrivalent vaccine
Group 2: Subjects who received 0.5 mL dose(s) of Fluzone Quadrivalent vaccine
[a] Fever is defined as body temperature of >= 100.4 F

Analyses of Immunogenicity by Age Group

Table 10. Subgroup Analysis by Age: Comparison of 2 Dose Levels of Fluzone Quadrivalent Vaccine (0.5 mL vs 0.25 mL) as Assessed by the Ratio of Geometric Mean Titers (GMTs) - Per-Protocol Analysis Set

Age Subgroup	Antigen Strain	Group 1 M/N	Group 1 GMT	Group 2 M/N	Group 2 GMT	Ratio of GMTs[a] (95% CI)
6 to < 24 months	A/H1N1	274/277	119	293/296	212	1.78 (1.32; 2.39)
6 to < 24 months	A/H3N2	277/277	130	201/296	201	1.54 (1.21; 1.97)
6 to < 24 months	B Victoria	274/277	157	179/296	217	1.38 (1.05; 1.82)
6 to < 24 months	B Yamagata	277/277	146	229/296	229	1.57 (1.22; 2.01)
24 to <36 months	A/H1N1	246/248	410	246/247	488	1.19 (0.96; 1.48)
24 to <36 months	A/H3N2	248/248	400	246/247	608	1.52 (1.13; 2.04)
24 to <36 months	B Victoria	246/248	460	246/247	611	1.33 (1.05; 1.67)
24 to <36 months	B Yamagata	247/248	428	247/247	577	1.35 (1.06; 1.7)

Source: sBLA 103914\6208: Appendix 15, Tables 31 and 32.
N: number of subjects analyzed according to the Per-Protocol Analysis Set and fulfilling column header
M: number of subjects with available data for the considered endpoint
CI: confidence interval
Group 1: Subjects who received 0.25 mL dose(s) of Fluzone Quadrivalent vaccine
Group 2: Subjects who received 0.5 mL dose(s) of Fluzone Quadrivalent vaccine
[a] Ratio of GMTs = GMT Group 2 divided by GMT Group 1

Table 11: Subgroup Analysis by Age: Comparison of 2 Dose Levels of Fluzone Quadrivalent Vaccine (0.5 mL vs 0.25 mL) as Assessed by Seroconversion Rates - Per-Protocol Analysis Set

Age Subgroup	Antigen Strain	Group 1 n/M	Group 1 SC rate[a] %	Group 2 n/M	Group 2 SC rate[a] %	Difference in SC rates[b] (95% CI)
6 to < 24 months	A/H1N1	181/245	73.9	205/252	81.3	7.5 (0.14; 14.7)
6 to < 24 months	A/H3N2	201/248	81	228/255	89.4	8.4 (2.16; 14.6)
6 to < 24 months	B Victoria	202/245	82.4	208/252	82.5	0.1 (-6.6; 6.8)
6 to < 24 months	B Yamagata	207/248	83.5	221/254	87	3.5 (-2.69; 9.8)
24 to <36 months	A/H1N1	190/225	84.4	201/231	87	2.6 (-3.89; 9.1)
24 to <36 months	A/H3N2	188/227	82.8	192/232	82.8	-0.1 (-7; 6.9)
24 to <36 months	B Victoria	208/225	92.4	220/231	95.2	2.8 (-1.7; 7.5)
24 to <36 months	B Yamagata	209/226	92.5	224/234	95.7	3.2 (-1.2; 7.9)

Source: sBLA 103914\6208: Appendix 15, Tables 33 and 34.
n: number of subjects analyzed according to the Per-Protocol Analysis Set and fulfilling column header
M: number of subjects with a valid serology result for the particular antigen, including results reported as < LLOQ or > ULOQ
LLOQ: lower limit of quantification; ULOQ: upper limit of quantification
CI: confidence interval
Group 1: Subjects who received 0.25 mL dose(s) of Fluzone Quadrivalent vaccine
Group 2: Subjects who received 0.5 mL dose(s) of Fluzone Quadrivalent vaccine
[a] SC (seroconversion) is defined as either a pre-vaccination hemagglutination inhibition titer < 1:10 and a post-vaccination titer >= 1:40 or a pre-vaccination titer >= 1:10 and at least a 4-fold increase in post-vaccination titer (considered separately for each strain)
[b] The difference in SC rates = SC rate of Group 2 minus SC rate of Group 1

Reviewer Comment: The subgroup analysis by age shows that while the point estimates for geometric mean titer (GMT) and seroconversion (SC) are generally slightly higher in the older age group, the GMT ratios and SC

rates are generally comparable. These data support the effectiveness of the 0.5 mL dose volume in both age groups.

6.1.11.4 Dropouts and/or Discontinuations

Analyses were performed on the safety and per-protocol analysis sets as defined in the study protocol by the applicant. Results were comparable when performed on the full analysis set, indicating that dropouts and discontinuations did not affect the study results.

6.1.11.5 Exploratory and Post Hoc Analyses

Analyses of Immunogenicity Among Seronegative Subjects (Pre-vaccination HAI titer <1:10

An additional analysis of immunogenicity endpoints was requested in seronegative subjects to assess for a difference in the immune response between the 0.25 mL and 0.5 mL doses. Results are outlined in Tables 12 and 13 below.

Table 12. Ratio of Geometric Mean Titers (GMTs) (0.5 mL vs 0.25 mL) Among Subjects with at least 1 Pre-Vaccination HAI Titer <1:10– Per Protocol Set.

Number of Doses	Antigen Strain	Group 1 (N=502) M	Group 1 (N=502) GMT	Group 2 (N=525) M	Group 2 (N=525) GMT	Ratio of GMTs[a] (95% CI)
1 Dose	A/H1N1	76	103	86	144	1.4 (0.906; 2.15)
1 Dose	A/H3N2	125	110	134	151	1.37 (0.95; 1.97)
1 Dose	B Victoria	47	89	53	124	1.4 (0.835; 2.34)
1 Dose	B Yamagata	45	103	46	134	1.29 (0.8; 2.09)
2 Doses	A/H1N1	162	104	171	207	1.99 (1.5; 2.66)
2 Doses	A/H3N2	184	146	196	260	1.78 (1.41; 2.24)
2 Doses	B Victoria	183	139	180	175	1.26 (0.94; 1.69)
2 Doses	B Yamagata	163	154	161	222	1.44 (1.09; 1.92
Overall	A/H1N1	238	104	257	183	1.77 (1.39; 2.25)
Overall	A/H3N2	309	130	330	208	1.6 (1.3; 1.96)
Overall	B Victoria	230	127	233	162	1.28 (0.99; 1.65)
Overall	B Yamagata	208	141	207	199	1.41 (1.1; 1.8)

Source: sBLA 103914\6208.5005: Conducted Analyses on Immunogenicity Endpoints, Table 9.13, p. 16-17.
M: number of subjects with available data for the considered endpoint

Group 1: Subjects who received 0.25 mL dose(s) of Fluzone Quadrivalent vaccine
Group 2: Subjects who received 0.5 mL dose(s) of Fluzone Quadrivalent vaccine
[a] Ratio of GMTs = $GMT_{Group\ 2}$ divided by $GMT_{Group\ 1}$

Table 13. Seroconversion Rates (0.5 mL vs 0.25 mL) Among Subjects with at least 1 Pre-vaccination HAI Titer < 1:10– Per-Protocol Analysis Set.

Number of Doses	Antigen Strain	Group 1 (N=502) N/M	Group 1 SC rate[a] %	Group 2 (N=525) n/M	Group 2 SC rate[a] %	Difference in SC rates[b] (95% CI)
1 Dose	A/H1N1	61/76	80.3	73/86	84.9	4.6 (**-7.06**; 16.6)
1 Dose	A/H3N2	97/125	77.6	116/134	86.6	9 (**0.39**; 18.3)
1 Dose	B Victoria	37/47	78.7	45/53	84.9	6.2 (**-8.96**; 21.6)
1 Dose	B Yamagata	37/45	82.2	41/46	89.1	6.9 (**-7.93**; 21.8)
2 Doses	A/H1N1	133/162	82.1	155/171	90.6	8.5 (**1.16**; 16)
2 Doses	A/H3N2	166/184	90.2	191/196	97.4	7.2 (**2.43**; 12.6)
2 Doses	B Victoria	159/183	86.9	154/180	85.6	-1.3 (**-8.52**; 5.83)
2 Doses	B Yamagata	145/163	89	150/161	93.2	4.2 (**-2.15**; 10.7)
Overall	A/H1N1	194/238	81.5	228/257	88.7	7.2 (**0.93**; 13.6)
Overall	A/H3N2	263/309	85.1	307/330	93	7.9 (**3.1**; 12.9)
Overall	B Victoria	196/230	85.2	199/233	85.4	0.2 (**-6.3**; 6.7)
Overall	B Yamagata	182/208	87.5	191/207	92.3	4.8 (**-1.1**; 10.7)

Source: Adapted from sBLA 103914\6208.5005: Conducted Analyses on Immunogenicity Endpoints, Table 9.17, p. 27-29.
n: number of subjects analyzed according to the Per-Protocol Analysis Set and fulfilling column header
M: number of subjects with a valid serology result for the particular antigen, including results reported as < LLOQ or > ULOQ
LLOQ: lower limit of quantification; ULOQ: upper limit of quantification
CI: confidence interval
Group 1: Subjects who received 0.25 mL dose(s) of Fluzone Quadrivalent vaccine
Group 2: Subjects who received 0.5 mL dose(s) of Fluzone Quadrivalent vaccine
[a] SC (seroconversion) is defined as either a pre-vaccination hemagglutination inhibition titer < 1:10 and a post-vaccination titer >= 1:40 or a pre-vaccination titer >= 1:10 and at least a 4-fold increase in post-vaccination titer (considered separately for each strain)
[b] The difference in SC rates = SC rate of Group 2 minus SC rate of Group 1

Reviewer Comment: Immunogenicity in the seronegative subjects is comparable to that of all subjects and met non-inferiority criteria for each strain.

6.1.12 Safety Analyses

6.1.12.1 Methods

All safety analyses were conducted with the Safety Analysis Set, which included all subjects who received either study vaccine. A total of 1950 subjects were enrolled, of whom 1941 (99.5%) were vaccinated and included in the safety analysis (see Table 5 in Section 6.1.10 for complete evaluation of subject disposition).

The collection of safety data included any immediate Adverse Reactions (ARs) within 20 minutes of vaccine administration, solicited local and systemic adverse reactions from Day 0-7, and unsolicited AEs and SAEs from Visit 1-2 for subjects receiving one dose of vaccine and from Visit 1-3 for subjects receiving two doses of vaccine. Participants were monitored for unsolicited adverse events for 28 days after each dose and for serious adverse events (SAEs) during the 6 months following the last dose.

Because of concerns regarding the integrity of safety data collected at Site 009 (refer to Section 3.2), an additional statistical analysis was conducted that excluded safety data collected at this site and results of that analysis were similar to the Safety Analysis Set.

6.1.12.2 Overview of Adverse Reactions and Adverse Events

Immediate unsolicited ARs (within 20 minutes of injection) were reported by 2 (0.2%) of subjects in Group 1 and no subjects in Group 2.

After any vaccination, similar percentages of subjects in Group 1 (645 [71%] subjects) and Group 2 (698 [74.2%] subjects) experienced a solicited adverse reaction. Within the 28 day follow-up period following the final vaccination, AEs leading to discontinuation occurred in 3 subjects (0.3%) in Group 1 and no subjects in Group 2.

Local solicited ARs within 7 days post-vaccination

Solicited injection site reactions were experienced by 480 (52.8%) subjects in Group 1 and 533 (56.8%) subjects in Group 2. For both vaccine groups, tenderness was the most frequently reported solicited injection site reaction (Group 1, 430 [47.3%] subjects; Group 2, 473 [50.4%] subjects), followed by redness (Group 1, 210 [23.1%] subjects; Group 2, 228 [24.3%] subjects) and swelling (Group 1, 117 [12.9%] subjects; Group 2, 138 [14.7%] subjects) Results were similar for subjects who received 1 or 2 doses of vaccine. Most subjects had solicited injection site reactions with onsets between Day 0 and Day 3 and lasting for 3 days or less.

Table 14. Solicited Local Adverse Reactions by Type and Severity Occurring within 7 Days of Vaccination – Safety Analysis Set.

Subjects experiencing at least one	Maximum Intensity	Group 1 (N=949) n/M (%)	Group 2 (N=992) n/M (%)
Tenderness	Any	430/909 (47.3)	473/939 (50.4)
Tenderness	Grade 1[a]	322/909 (35.4)	347/939 (37)
Tenderness	Grade 2[b]	93/909 (10.2)	115/939 (12.2)
Tenderness	Grade 3[c]	15/909 (1.7)	11/939 (1.2)
Redness	Any	210/909 (23.1)	228/938 (24.3)
Redness	Grade 1[a]	204/909 (22.4)	220/938 (23.5)
Redness	Grade 2[b]	6/909 (0.7)	6/938 (0.6)
Redness	Grade 3[c]	0/909 (0)	2/938 (0.2)
Swelling	Any	117/908 (12.9)	138/937 (14.7)
Swelling	Grade 1[a]	114/908 (12.6)	130/937 (13.9)
Swelling	Grade 2[b]	2/908 (0.2)	8/937 (0.9)
Swelling	Grade 3[c]	1/908 (0.1)	0/937 (0)

Source: Adapted from: sBLA 103914\6208; GRC88 Clinical Study Report, Table 5.4, p 94.

N: number of subjects analyzed according to the Safety Analysis Set and fulfilling column header

n: number of subjects experiencing the endpoint listed

M: number of subjects with available data for the relevant endpoint

CI: confidence interval; MedDRA version: 19.0

Group 1: Subjects who received 0.25 mL dose(s) of Fluzone Quadrivalent vaccine

Group 2: Subjects who received 0.5 mL dose(s) of Fluzone Quadrivalent vaccine

[a]Grade 1: Tenderness: Minor reaction when injection site is touched; Redness, swelling: >0 to < 25 mm

[b] Grade 2: Tenderness: Cries or protests when injection site is touched; Redness, swelling: ≥ 25 to < 50 mm

[c]Grade 3 - Tenderness: Cries when injected limb is moved, or the movement of the injected limb is reduced; Injection-site redness, Injection-site swelling: ≥ 50 mm

Reviewer Comment: The percentages of solicited local (injection site) adverse reactions, including grade 3 reactions, are balanced between the treatment groups.

Systemic solicited adverse reactions within 7 days post-vaccination

The rate of solicited systemic reactions was similar in both groups (Group 1, 533 [58.6%] subjects; Group 2, 561 [59.6%] subjects). Solicited systemic adverse reactions trended higher in subjects who received 2 doses of study vaccine (Group 1, 61.8%; Group 2, 62.6%) than subjects who received 1 dose of study vaccine (Group 1, 54.7%; Group 2, 56.0%)

Irritability (Group 1, 430 [47.4%] subjects; Group 2, 457 [48.6%] subjects) was the most frequently reported solicited systemic reaction in both vaccine groups. Abnormal crying (Group 1, 302 [33.3%] subjects; Group 2, 321 [34.1%] subjects), drowsiness (Group 1, 290 [31.9%] subjects; Group 2, 294 [31.3%] subjects), and loss of appetite (Group 1,

248 [27.3%] subjects; Group 2, 266 [28.3%] subjects) were experienced by similar percentages of subjects in each vaccine group. Any fever was experienced by 101 (11.3%) subjects in Group 1 and 113 (12.2%) subjects in Group 2. Solicited systemic adverse reactions occurred within 3 days of vaccination in most subjects and lasted for 3 days or less. See Table 15 below.

Table 15. Systemic Adverse Reactions by Type and Severity Occurring within 7 Days of Vaccination – Safety Analysis Set.

Subjects experiencing at least one:	Maximum Intensity	Group 1 (N=949) n/M (%)	Group 2 (N=992) n/M (%)
Fever	Any	101/893 (11.3)	113/930 (12.2)
Fever	Grade 1[a]	50/893 (5.6)	59/930 (6.3)
Fever	Grade 2[b]	46/893 (5.2)	43/930 (4.6)
Fever	Grade 3[c]	5/893 (0.6)	11/930 (1.2)
Vomiting	Any	90/908 (10)	96/940 (10.2)
Vomiting	Grade 1[a]	49/908 (5.4)	61/941 (6.5)
Vomiting	Grade 2[b]	38/908 (4.2)	30/941 (3.2)
Vomiting	Grade 3[c]	4/908 (0.4)	5/941 (0.5)
Abnormal crying	Any	302/908 (33.3)	321/941 (34.1)
Abnormal crying	Grade 1[a]	192/908 (21.1)	202/941 (21.5)
Abnormal crying	Grade 2[b]	82/908 (9)	95/941 (10.1)
Abnormal crying	Grade 3[c]	28/908 (3.1)	24/941 (2.6)
Drowsiness	Any	290/908 (31.9)	294/940 (31.1)
Drowsiness	Grade 1[a]	209/908 (23)	229/940 (24.4)
Drowsiness	Grade 2[b]	62/908 (6.8)	50/940 (5.3)
Drowsiness	Grade 3[c]	19/908 (2.1)	15/940 (1.6)
Loss of Appetite	Any	248/908 (27.3)	266/940 (28.3)
Loss of Appetite	Grade 1[a]	164/908 (18.1)	188/940 (20)
Loss of Appetite	Grade 2[b]	71/908 (7.8)	57/940 (6.1)
Loss of Appetite	Grade 3[c]	13/908 (1.4)	21/940 (2.2)
Irritability	Any	430/908 (47.4)	457/940 (48.6)
Irritability	Grade 1[a]	228/908 (25.1)	252/940 (26.8)
Irritability	Grade 2[b]	169/908 (18.6)	167/940 (17.8)
Irritability	Grade 3[c]	33/908 (3.6)	38/940 (4)

Source: Adapted from: sBLA 103914\6208; GRC88 Clinical Study Report, Table 5.5, p 96-97.

N: number of subjects analyzed according to the Safety Analysis Set and fulfilling column header

n: number of subjects experiencing the endpoint listed

M: number of subjects with available data for the relevant endpoint

CI: confidence interval; MedDRA version: 19.0

Group 1: Subjects who received 0.25 mL dose(s) of Fluzone Quadrivalent vaccine

Group 2: Subjects who received 0.5 mL dose(s) of Fluzone Quadrivalent vaccine

[a]Grade 1: Fever: ≥ 100.4°F to ≤ 101.3°F; Vomiting: 1 episode per 24 hours; Abnormal crying: < 1 hour; Drowsiness: Sleepier than usual or less interested in surroundings; Loss of Appetite: Eating less than normal; Irritability: Easily consolable
[b] Grade 2: Fever: > 101.3°F to ≤ 103.1°F; Vomiting: 2-5 episodes per 24 hours; Abnormal crying: 1-3 hours; Drowsiness: Not interested in surroundings or did not wake up for a feed/meal; Loss of Appetite: Missed 1 or 2 feeds/meals completely; Irritability: Requiring increased attention
[c] Grade 3: Fever: > 103.1°F; Vomiting: ≥ 6 episodes per 24 hours; Abnormal crying: > 3 hour; Drowsiness: Sleeping most of the time or difficult to wake up; Loss of Appetite: Refuses ≥ 3 feeds/meals or refuses most feeds/meals; Irritability: Inconsolable

Reviewer Comment: Overall, the solicited systemic ARs were balanced between the treatment groups. The one imbalance noted was the Grade 3 fever rate which was 0.6% in Group 1 and 1.2% in Group 2. Additional subgroup analyses to further investigate the difference in Grade 3 fevers between treatment groups are presented in Table 16 below.

Table 16. Subgroup Analysis by Age: Fever Intensity and Action Taken for Fever – Safety Analysis Set.

Age Group			Group 1 n/N	Group 1 % (95% CI)	Group 2 n/N	Group 2 % (95%CI)
6 to <24 months	**Fever Intensity**	**Any (≥100.4ºF)**	60/498	12 (9.3; 15.2)	83/530	15.7 (12.7; 19)
6 to <24 months	**Fever Intensity**	**Grade 3 (>103.1ºF)**	4/498	0.8 (0.2; 2)	10/530	1.9 (0.9; 3.4)
6 to <24 months	**Action Taken for Fever**	**Medication**	32/498	6.4 (4.4; 9)	40/530	7.5 (5.4; 10.1)
6 to <24 months	**Action Taken for Fever**	**HCP Contact**	1/498	0.2 (0; 1.1)	2/530	0.4 (0; 1.4)
6 to <24 months	**Action Taken for Fever**	**Hospitalization**	0/498	0 (0; 0.7)	0/530	0 (0; 0.7)
24 to < 36 months	**Fever Intensity**	**Any (≥100.4ºF)**	41/395	10.4 (7.6; 13.8)	10/399	1.9 (0.9; 3.4)
24 to < 36 months	**Fever Intensity**	**Grade 3 (>103.1ºF)**	1/395	0.3 (0; 1.4)	1/399	0.3 (0; 1.4)
24 to < 36 months	**Action Taken for Fever**	**Medication**	25/395	6.3 (4.1; 9.2)	18/399	4.5 (2.7; 7)
24 to < 36 months	**Action Taken for Fever**	**HCP Contact**	0/395	0 (0; 0.9)	1/399	0.3 (0; 1.4)
24 to < 36 months	**Action Taken for Fever**	**Hospitalization**	0/395	0 (0; 0.9)	0/399	0 (0; 0.9)

Source: sBLA 103914\6208: Addendum to the GRC88 Clinical Study Report, Table 9.7, and Appendix 15, Tables 70 and 71.
n: number of subjects experiencing the endpoint listed
N: number of subjects analyzed according to the Safety Analysis Set and fulfilling the column header
CI: confidence interval
HCP: health care provider
Group 1: Subjects who received 0.25 mL dose(s) of Fluzone Quadrivalent vaccine
Group 2: Subjects who received 0.5 mL dose(s) of Fluzone Quadrivalent vaccine

> ***Reviewer Comment: A subgroup analysis of the grade 3 fever rates by age revealed that this increased grade 3 fever rate was driven by the 6 to < 24 month age group in which grade 3 fever was 0.8% in Group 1 and 1.9% in Group 2, whereas the grade 3 fever rate in subjects 24 to < 36 months of age was equal at 0.3% for both Group 1 and 2. Despite the higher fever rates and grade 3 fevers seen in the 6 to < 24 month age group, there were no significant differences in rates of medication use, contact with a health care provider or hospitalization between treatment groups or age subgroups. Thus, the higher rates of fever did not correspond with a need for additional medical care and were of uncertain clinical significance.***

Unsolicited AEs

After any vaccination, 5 immediate ARs, within 20 minutes of vaccine injection, were experienced between a total of 2 (0.2%) subjects in Group 1 (diarrhea in one subject and venipuncture site bruising, erythema, pain and swelling in the other subject). No subjects in Group 2 experienced immediate AEs. None of these immediate AEs led to study discontinuation.

After any vaccine injection, rates of unsolicited AEs trended slightly higher in Group 1 subjects (43.9%) than in Group 2 subjects (39.7%). The most frequently reported unsolicited AEs after any vaccination were in the Infections and infestations System Organ Class (SOC) (Group 1, 193 [20.3%] subjects; Group 2, 201 [20.3%] subjects), followed by Respiratory, thoracic and mediastinal disorders (Group 1, 150 [15.8%] subjects; Group 2, 154 [15.5%] subjects). By preferred term, the most commonly reported unsolicited AEs were cough (Group 1, 104 [11.0%] subjects; Group 2, 103 [10.4%] subjects) and rhinorrhea (Group 1, 72 [7.6%] subjects; Group 2, 71 [7.2%] subjects). The majority of unsolicited AEs were Grade 1 or 2 in intensity. Grade 3 unsolicited non-serious AEs were experienced by 62 (6.5%) subjects in Group 1 and 65 (6.6%) subjects in Group 2; of these Grade 3 unsolicited non-serious AEs, 2 subjects in each Group were thought to be related to the vaccine by investigators (Group 1: one subject with cough, rhinorrhea, sneezing and one subject with dehydration, diarrhea; Group 2: one subject with an injection site bruise and one subject with cough).

6.1.12.3 Deaths

There were no deaths reported in this study.

6.1.12.4 Nonfatal Serious Adverse Events

Serious adverse events were collected between Visit 1 and Visit 2 for subjects receiving 1 dose and between Visit 1 and Visit 3 for subjects receiving 2 doses. A total of 5 (0.5%) subjects in Group 1 and 5 (0.5%) subjects in Group 2 experienced 10 SAEs. One

subject discontinued the study due to the SAE, but the event was considered not related to the study vaccine, and one subject had an SAE considered related to the study vaccine but continued in the study; both of these subjects were in Group 1.
In Group 1, one subject was discontinued from the study due to pneumonia that was diagnosed 21 days after 1 dose of the study vaccine; the pneumonia was considered unrelated to the study vaccine. The other SAEs in Group 1 included: a hospitalization for a known diagnosis of tracheomalacia, a hospitalization for tonsillitis 27 days after the study vaccine, a hospitalization for acute viral upper respiratory infection 9 days following study vaccine, and a diagnosis of chronic urticaria with ongoing symptoms for more than 6 weeks prior to study vaccination and a rash and wheals 3 days after 1 dose of study vaccine (based on a protocol definition of SAE that included any hypersensitivity/allergic reaction). These four subjects with SAEs continued in the study, and the event of chronic urticaria was considered related to the study vaccine.
In Group 2, all five of the subjects who experienced an SAE continued in the study, and none of the events were considered related to the study vaccine. The SAEs in Group 2 included: an abscess of the right medial thigh 13 days following study vaccine that resolved followed by a cellulitis on the right buttocks requiring hospitalization, a hospitalization for dehydration due to herpangina that started 6 days following study vaccine, a hospitalization for RSV bronchiolitis 19 days following study vaccine, a hospitalization for management of an accidental clonidine ingestion 27 days following study vaccine, and a hospitalization for pneumonia 28 days following study vaccine.
There were no febrile seizures reported for this study.

> ***Reviewer Comment: The rates of SAEs were balanced between the study arms. The SAEs that occurred were not considered related to study vaccination except for 1 case of chronic urticaria.***
> ***The reviewer agrees with the investigators' assessments of relatedness, with the exception of the assessment that the case of chronic urticaria was related to the study vaccine. The subject had symptoms for at least 6 weeks prior to receiving the study vaccine. It seems likely that access to immediate medical care in the study facilitated the diagnosis, but that the diagnosis was not related to the study vaccine.***
> ***Although there were no febrile seizures detected in this study, the study was not adequately powered to evaluate for the outcome of febrile seizure. A much larger safety database would be needed to evaluate the risk of febrile seizure, and routine pharmacovigilance is adequate to monitor for this risk.***

6.1.12.6 Clinical Test Results

There were no clinical laboratory evaluations in this study.

6.1.12.7 Dropouts and/or Discontinuations

Two (0.2%) subjects in Group 1 (one due to an unknown AE and one due to pneumonia diagnosed 21 days after vaccination) discontinued the study due to a non-serious AE. One subject (0.1%) in Group 1 (due to pneumonia diagnosed 28 days after vaccination) discontinued due to an SAE. The 2 events of pneumonia were considered to be unrelated to study vaccine given the timing of diagnoses; the relationship of the unknown AE to vaccination could not be assessed. No subjects in Group 2 discontinued due to an AE. The small numbers of dropouts and discontinuations in each group did not likely affect the results of the safety evaluations.

6.1.13 Study Summary and Conclusions

Study GRC88 was a Phase 4, randomized, observer-blind, 2-arm, multi-center study to evaluate the safety and immunogenicity of 2 different dose levels (0.25 mL and 0.5 mL) of Fluzone Quadrivalent influenza vaccine (QIV) in healthy children 6 to < 36 months of age conducted at 38 sites in the United States. The demographic characteristics were similar between the treatment groups.
Of the 1950 subjects enrolled, 1941 were vaccinated, of which 949 received the 0.25 mL dose of Fluzone QIV and 992 received the 0.5 mL dose of Fluzone QIV. Subjects received one or two doses of study vaccine per ACIP guidelines. A subset of subjects had blood drawn at baseline and 28 days following final study vaccine for evaluation HAI titers. Local and systemic reactogenicity was captured by diary card for 7 days post-vaccination; SAEs were assessed through 28 days following final study vaccination.
The primary endpoint of non-inferiority of fever rates was demonstrated for the 0.25 mL dose(s) of Fluzone QIV compared to the 0.5 mL dose(s) of Fluzone QIV. The secondary endpoints of immunologic non-inferiority for all four vaccine strains were demonstrated for the 0.5 mL dose(s) of Fluzone QIV compared to the 0.25 mL dose(s) of Fluzone QIV by Geometric Mean Titer ratios and seroconversion rate differences.
Local and systemic reactogenicity were balanced between treatment arms. There were no withdrawals due to adverse events. There was no imbalance of serious adverse events between the two study arms, and no deaths occurred during the study.
The available safety and immunogenicity data support updating the dosing regimen to include the 0.5 mL dose volume of Fluzone QIV for children 6 to < 36 months of age, for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine, in addition to the currently approved 0.25 mL dose volume of Fluzone QIV.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

There were no pregnancies reported in this study as it was conducted in a pediatric age group. There are insufficient data to establish whether there is a vaccine-associated risk with Fluzone Quadrivalent in pregnant women.

9.1.2 Use During Lactation

There were no data collected regarding use during lactation in this study as it was conducted in a young pediatric age group. There was no information provided on the presence of Fluzone Quadrivalent in human milk, the effects on the breastfed infant, or the effects on milk production.

9.1.3 Pediatric Use and PREA Considerations

Fluzone QIV is currently approved for use in persons 6 months of age and older; currently the dose volume in children 6 to < 36 months of age is 0.25 mL, and in persons 3 years of age and older, the dose volume is 0.5 mL. The manufacturer was granted a partial waiver for infants <6 months of age based on the reasoning that Fluzone Quadrivalent would provide no meaningful therapeutic benefit over vaccination beginning at 6 months of age, and these vaccines are unlikely to be used by a substantial number of infants <6 months of age (Section 505B(a)(4)(A)iii of the Food

Drug and Cosmetic Act). The applicant has previously fulfilled all pediatric study assessments for this product for children 36 months of age and older because the 0.5 mL dose volume is licensed for use in this age group. With the data submitted to this supplement, the applicant has fulfilled the pediatric assessment in individuals 6 to <36 months of age.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 17. Risk Benefit Considerations for the 0.5 mL dose of Fluzone QIV in Children 6 to <36 months of age.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Influenza virus infection is a major cause of morbidity and mortality. • Children are a high-risk group for developing complications associated with influenza virus infection. • Influenza vaccination has been shown to be effective in reducing the incidence of influenza-like illness (ILI), hospitalization for influenza/pneumonia/other respiratory conditions, acute complications among high-risk patients, and mortality from all causes.	• Influenza virus infection is a potentially life-threatening disease. • Influenza virus infection is a serious condition, particularly in children who are high-risk for developing complications including death.
Unmet Medical Need	• Only Fluzone/Fluzone Quadrivalent, Fluarix/Fluarix Quadrivalent, FluLaval/FluLaval Quadrivalent and Afluria/Afluria Quadrivalent are approved for use in infants and children ages 6 to < 36 months. • Live attenuated influenza vaccine (FluMist) is approved for persons ages ≥ 2 to < 50 years.	• Vaccine shortages could lead to delays or lapses in annual vaccination in children. • Additional availability of an 0.5 mL dose of Fluzone Quadrivalent for infants and children 6 to < 36 months of age would allow better vaccine coverage in this vulnerable age group and facilitate implementation of influenza vaccination program.
Clinical Benefit	• Clinical trial GRC88 in children 6 to < 36 months of age demonstrated immunologic non-inferiority of the 0.5 mL dose volume compared to the 0.25 mL dose volume was demonstrated in terms of 28 day HAI GMT ratios and seroconversion rate differences.	• Non-inferiority criteria for immunogenicity used in this evaluation are well recognized and appropriate for this evaluation and support the clinical effectiveness.
Risk	• Clinical trial GRC88 demonstrated non-inferiority of fever rate following the licensed Fluzone QIV 0.25 mL dose volume compared to the higher 0.5 mL dose volume • The most substantial risks of vaccination with Fluzone QIV were mild local and systemic reactogenicity.	• The risks of vaccination with the 0.5 mL dose of Fluzone QIV appear to be minor, and similar to those associated with the 0.25 mL dose of Fluzone QIV in children 6 to <36 months of age.
Risk Management	• The package insert describes in detail the common systemic and injection site reactions. Rarely observed conditions following influenza vaccination, such as Guillain-Barre Syndrome, are also cited.	• The package insert and the current pharmacovigilance plan are adequate to manage these risks.

11.2 Risk-Benefit Summary and Assessment

Data submitted to sBLA 103914\6208 establish the safety and effectiveness of Fluzone Quadrivalent (0.5 mL per dose) in children 6 to < 36 months of age. The risks of vaccination with 0.5 mL per dose of Fluzone QIV in children 6 to < 36 months of age have been found to be minimal. Thus, the overall risk/benefit profile of this product is favorable in this age group.

11.4 Recommendations on Regulatory Actions

Fluzone QIV (0.5 mL per dose) is recommended for approval in children 6 to < 36 months of age for active immunization for the prevention of disease caused by the influenza A subtype viruses and type B viruses contained in the vaccine.

11.5 Labeling Review and Recommendations

Negotiations and CBER recommendations resulted in the following changes to the current label for Fluzone Quadrivalent:

- In the Highlights of Prescribing Information, CBER requested that the Applicant remove one bullet point under the subsection titled “Use in Specific Populations” indicating that safety and effectiveness have not been established in pregnant women and children under 6 months of age.
- In Section 6.1, Clinical Trials Experience, CBER requested that the Applicant create Table 4, describing overall rates of local and systemic reactogenicity from Study GRC88 so that they specifically described rates of grade 3 adverse reactions. CBER considered the severe reactions to be clinically important information for prescribers. Also, all references to deaths in clinical studies were removed because they were not vaccine related, and thus not relevant.
- In Section 6.2 entitled Postmarketing Experience, the Applicant updated the information to reflect safety reports occurring for both Fluzone (trivalent) and Fluzone Quadrivalent because the formulation of these products is identical except for the one additional influenza B strain contained in the quadrivalent formulation.
- In Section 8.1 entitled Pregnancy was updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR).
- In Section 14.4, the immunogenicity results from Study GRC88 were added in text format.
- Minor edits for clarity and formatting were made throughout the label.

11.6 Recommendations on Postmarketing Actions

No changes to the submitted pharmacovigilance plan for Fluzone QIV are recommended based on the information contained in this application.