Application Type	Efficacy Supplement
STN	103914/5574
CBER Received Date	August 10, 2012
PDUFA Goal Date	June 10, 2012
Division / Office	DVRPA/OVRR
Priority Review	No
Reviewer Name(s)	Niranjan Bhat, M.D., M.H.S. Medical Officer, Clinical Review Branch 1
Review Completion Date / Stamped Date	June 7, 2013
Supervisory Concurrence	Jeffrey Roberts, M.D. Chief, Clinical Review Branch 1
Applicant	Sanofi Pasteur, Inc.
Established Name	Influenza Virus Vaccine
(Proposed) Trade Name	Fluzone Quadrivalent
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Liquid suspension for injection Each 0.5 mL dose contains 15 µg of influenza hemagglutinin protein (60 µg total) from each of the following four influenza subtypes or lineages: • A/H1N1 • A/H3N2 • B Victoria • B Yamagata Other ingredients: • Sodium phosphate-buffered isotonic sodium chloride solution • Formaldehyde • Octylphenol Ethoxylate
Dosage Form(s) and Route(s) of Administration	Supplied in three presentations: • 0.5 mL prefilled single-dose syringe (for individuals 3 years of age and older) • 0.5 mL single-dose vial (for individuals 3 years of age and older) • 0.25 mL prefilled single-dose syringe (for individuals 6 months through 35 months of age)
Dosing Regimen	• 6 months through 8 years of age: 1 or 2 doses, based on vaccination history • 9 years of age and older: 1 intramuscular dose
Indication(s) and Intended Population(s)	Indicated for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.

	Fluzone Quadrivalent is intended for use in persons 6 months of age and older.

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GLOSSARY

GLOSSARY

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
AESI	Adverse Events of Special Interest
AR	Adverse Reaction
BIMO	CBER Bioresearch Monitoring
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use (EMA)
CI	Confidence Interval
CFR	Code of Federal Regulations
CRF	Case Report Form
CSR	Clinical Study Report
dil	Dilution
QIV	Fluzone Quadrivalent
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
GMT	Geometric Mean Titer
GMTR	Geometric Mean Titer Ratio
HA	Hemagglutinin
HAI	Hemagglutination Inhibition Assay
ICH	International Conference on Harmonisation
IND	Investigational New Drug application
IVRS	Interactive Voice Response System
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
PI	Package Insert
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PP	Per-protocol Analysis Set
PREA	Pediatric Research Equity Act
PT	Preferred Term
SAE	Serious Adverse Event
SAS	Safety Analysis Set
sBLA	Supplemental Biologics License Application
SCR	Seroconversion Rate
SOC	System Organ Class
STN	Submission Tracking Number
TIV	Trivalent inactivated influenza vaccine
US	United States
VRBPAC	Vaccines and Biological Products Advisory Commitee
WHO	World Health Organization

1. EXECUTIVE SUMMARY

Fluzone® trivalent inactivated influenza vaccine (TIV) is currently licensed for the prevention of influenza in persons 6 months of age and older. With this supplement, Sanofi Pasteur is seeking

approval for Fluzone Quadrivalent Influenza Vaccine, a quadrivalent, inactivated seasonal influenza vaccine indicated for active immunization against influenza disease caused by influenza A subtypes and type B viruses contained in the vaccine. Fluzone Quadrivalent (QIV) is manufactured using the same process as the currently licensed Fluzone trivalent vaccine, with a type B strain of a second lineage added to the seasonal TIV formulation. QIV therefore contains antigens from two influenza A subtype viruses (representing the H1N1 and H3N2 subtypes) and two type B viruses (representing the B/Victoria and B/Yamagata lineages). The applicant is pursuing licensure of QIV as a supplement to the existing Fluzone vaccine license based on demonstration of non-inferior immunogenicity and comparable safety with respect to Fluzone TIV. This supplement is intended to support the safety and effectiveness of QIV in persons 6 months of age and older.

The application included safety and immunogenicity data from three clinical trials: 1) a randomized, controlled, open-label phase 2 study in adults 18 years of age and older (GRC43); 2) a randomized, controlled, observer-blinded phase 3 study in elderly adults 65 years of age and older (QIV03); and 3) a randomized, controlled, observer-blinded phase 3 study in children aged 6 months to less than 9 years (QIV04). All studies were conducted in the United States. The development program accrued clinical data in all age groups for which the vaccine is intended for use (persons 6 months of age and older), with the exception of subjects 9 to 18 years of age. CBER agreed that, depending on our review of the resulting data in subjects <9 years of age, those data could be extrapolated to support use in subjects 9 to 18 years of age.

For all three trials, the primary endpoints for each strain were the ratios of the post-vaccination geometric mean titer (GMT) of hemagglutination inhibition (HAI) in the QIV treatment group to the post-vaccination GMT against the corresponding strain in the TIV treatment group. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio of the post-vaccination GMTs (QIV/TIV) was >0.66 for each of the four virus strains. Seroconversion rates (SCR) for each of the four strains were co-primary endpoints in Study QIV04. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference in SCR (QIV - TIV) post-vaccination was >-10%. Titers were measured 21 days (for Studies GRC43 and QIV03) or 28 days (for Study QIV04) after the final vaccination.

Across all 3 studies, 3307 subjects received QIV, 1239 subjects received a licensed Fluzone TIV, and 946 subjects received Investigational TIV. GRC43 and QIV03 had higher proportions of females (67.2% and 55.7%, respectively) compared to QIV04 (49.3%), as well as higher proportions of White subjects (88.4% and 89.5% vs. 58.3%).

Summary of Clinical Findings

Study GRC43 was a Phase 2, randomized, open-label, controlled, multi-center trial in which 570 adult subjects aged 18 years and older (half 18-60 years and half >60 years) were randomized (1:1:1) to receive QIV, the 2008-2009 licensed Fluzone vaccine, or the 2009-2010 licensed Fluzone vaccine.

Study QIV03 was a Phase 3, randomized, observer-blinded, controlled, multi-center trial in which 675 adults subjects aged 65 years and older were randomized (1:1:1) to receive QIV, the 2010-2011 licensed Fluzone TIV vaccine, or an investigational TIV vaccine containing the same two A strains plus the alternate lineage B strain contained in QIV.

Study QIV04 was a Phase 3, randomized, observer-blinded, controlled, multi-center trial in which 4363 children aged 6 months through 8 years were randomized (4:1:1) to receive QIV, the licensed 2010-2011 Fluzone TIV vaccine, or Investigational TIV. Subjects received one or two IM

doses (28 days apart), based on ACIP recommendations. Children 6 through 35 months of age received a 0.25 mL dose, while those aged 3 years and older received a 0.5 mL dose.

Overall, in comparing QIV to the TIV vaccines, non-inferiority criteria were met in Studies QIV03 and QIV04 for all strains in all age groups on the primary endpoints based on the ratio of geometric mean titers (GMTs) against all four strains. Criteria for demonstrating the superiority of QIV B strain responses compared to the cross-reactive responses generated by the TIV containing the non-corresponding B strain lineage were met for both strains in all age groups based on GMT ratios, with the exception of the B/Victoria strain in QIV03.

Safety data showed that solicited adverse reactions associated with QIV occurred at similar rates compared with trivalent formulations, including the previously licensed vaccines, for all age groups. There was no evidence that QIV administration resulted in increased reactogenicity compared to TIV, as might be suspected due to its higher antigen content. No imbalances in the frequency or severity of unsolicited adverse events were observed among the treatment arms within each study, and serious or uncommon conditions were not observed at abnormally high frequencies in any 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.

Studies were conducted in pediatric subjects from 6 months through 8 years of age. The safety and immunogenicity of QIV for the population 9-17 years of age will be extrapolated from the results of Studies QIV04 and GRC43. Extrapolation of these data is supported by previous experience regarding the safety and immunogenicity of inactivated influenza vaccines in this age group.

The pediatric development plan for Fluzone Quadrivalent was presented to the Pediatric Review Committee on April 3, 2013, and the Committee concurred with CBER's assessment.

Recommendation for Regulatory Action

In the opinion of the clinical reviewer, the clinical data submitted by the Applicant support the approval of Fluzone Quadrivalent for active immunization of persons 6 months of age and older against influenza disease caused by the influenza subtypes A and type B viruses contained in the vaccine.

Recommendation on Postmarketing Action

No safety signals were identified in the pre-licensure data. In the opinion of the clinical reviewer, no postmarketing requirement for additional safety studies is necessary.

The applicant submitted a pharmacovigilance plan to establish a pregnancy exposure registry as a postmarketing commitment. The applicant proposed to encourage pregnant women exposed to QIV (or their health care providers) to register at the time of exposure. Participants would be recruited by providing contact information in the Prescribing Information and Patient Information Sheet, as well as on a company-sponsored website and pregnancy outcomes will be sought via questionnaires sent to the reporter. Annual reports will be submitted with the Periodic Benefit-Risk Evaluation Report for Fluzone Quadrivalent, and a final study report will be submitted after the collection of six years of data. The proposed design of the pregnancy registry is acceptable.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition Studied

Influenza, a respiratory and systemic illness caused by influenza virus infection, is an important cause of infectious morbidity and mortality worldwide. Annual influenza epidemics are responsible for an estimated 3 to 5 million cases of severe respiratory illness, and about 250,000 to 500,000 deaths worldwide each year[1]. In the United States, an estimated 55,000 to 431,000 hospitalizations[2] and 3,000 to 49,000 deaths[3] are attributed to influenza each year. Influenza causes morbidity in all ages, with the highest attack rates in children, and the highest rates of serious morbidity and death among the elderly (who account for 90% of influenza-attributable deaths in the US), infants and young children, and persons with specific underlying medical conditions, such as chronic pulmonary or cardiac disease[4].

Influenza viruses are single, negative-stranded RNA viruses of the *Orthomyxoviridae* family. Humans are primarily affected by two influenza virus types, A and B. Influenza A viruses are further categorized into subtypes based upon their two primary surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA). Type B influenza viruses are comprised of a single HA and NA subtype. Since 1977, influenza A/H1N1 and A/H3N2 viruses and influenza B viruses have circulated globally. Generally, one strain from a specific type or subtype is the predominant circulating virus, while representative strains from the other two groups co-circulate at lower rates. Each year, global surveillance data are reviewed to predict which strains are likely to circulate in the following influenza season, and three are chosen for inclusion in the vaccine. Methods for predicting the next season's circulating strains are not always successful, and years in which the vaccine strains are not well matched to the season's strains continue to occur.

In addition, over the past 20 years, two antigenically distinct B virus lineages, known as B/Victoria and B/Yamagata, have alternated in circulation. Since 2001, the two lineages have co-circulated during each influenza season in the United States, usually with one lineage predominating over the other in most seasons[5]. Public health agencies have only been able to predict the prevailing B lineage roughly half of the time. Even during seasons in which the vaccine is matched to the more common lineage, B viruses of the alternate lineage can still represent a significant minority of circulating strains.

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.

1 World Health Organization, 2009
2 Thompson, 2004
3 Centers for Disease Control and Prevention, 2010
4 Fiore, 2010
5 Reed, 2012

2.2 Currently Available, Pharmacologically Unrelated Treatments for the Proposed Indication

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.

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 HA and 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. Currently, eight inactivated split-virus influenza vaccines are licensed in the U.S., including the trivalent formulation of Fluzone. Of these, only four are approved for individuals less than 18 years of age, and Fluzone is the only vaccine approved for children 6 through 23 months of age. A recent meta-analysis of 31 studies conducted between 1967 and 2011 calculated a pooled efficacy of 59% in healthy adults against laboratory-confirmed influenza illness[6]. Data regarding the efficacy of vaccination against influenza-related hospitalization and other severe outcomes also indicate that some protection is conferred[7].

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).[8]. 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 (Prevnar 13).[9]

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.

In the past year, two influenza vaccines manufactured by methods that do not rely on growth of influenza virus in eggs have been licensed in the U.S. Flucelvax is an inactivated subunit vaccine prepared from influenza virus propagated in a continuous cell line. Flublok is a recombinant protein vaccine containing HA proteins produced in a continuous insect cell line using a baculovirus vector. Both vaccines are indicated for use in adults, but not children.

6 Osterholm, 2012
7 Castilla, 2013; Talbot, 2011; Talbot, 2013;
8 Institute of Medicine, 2012
9 Leroy, 2012; Tse, 2012; Broder, 2012

2.4 Previous Human Experience with the Product

Fluzone Quadrivalent has not been licensed by any other regulatory authorities. However, 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 identical to 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

Sanofi Pasteur first submitted IND 14078 for Fluzone Quadrivalent on July 22, 2009. The original submission contained the protocol for Study GRC43. End-of-phase 2 advice was provided in a meeting on August 13, 2010, after which the sponsor conducted Study QIV03 (October-December 2010) and Study QIV04 (November 2010-January 2012). During that meeting, CBER recommended that GMT ratios and seroconversion rates should be made co-primary immunogenicity endpoints for the demonstration of non-inferiority. Sanofi proposed to use only GMT ratios as a primary endpoint for Study QIV03, with seroconversion rates as supporting data. CBER maintained the position that evaluation of both measures as co-primary endpoints would be preferable, but determined that Sanofi's proposal may be acceptable, since the pediatric study (QIV04) would be adequately powered to assess these parameters as co-primary endpoints. Also, it was agreed that manufacturing consistency of the drug substance and clinical consistency of the drug product would not be required, since the vaccine would be produced using currently validated and licensed processes, and that the safety and immunogenicity for children 9 through 17 years of age could be extrapolated from the pediatric and adult studies. This supplement for a quadrivalent formulation was submitted to the Fluzone BLA (STN 103914/5574) on August 9, 2012.

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 were conducted in accordance with Good Clinical Practice, the Declaration of Helsinki, International Conference on Harmonisation (ICH) 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.

CBER Bioresearch Monitoring (BIMO) conducted four clinical investigator inspections covering Studies QIV03 and QIV04 in support of this supplement. The inspections were conducted in accordance with FDA's Compliance Program Guidance Manual 7348.811, Inspection Program for Clinical Investigators. These inspections did not reveal any issues that would impact the data submitted to the supplement. Please see the review by Erin McDowell, Consumer Safety Officer, Bioresearch Monitoring Branch, Division of Inspections and Surveillance, Office of Compliance and Biologics Quality, for details.

3.3 Financial Disclosures

In accordance with 21 CFR § 54, Sanofi Pasteur submitted FDA Form 3454 with this supplement, certifying that, with the exception of one investigator, 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, with the exception of one individual, no investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

The applicant states that one individual reported receiving (b)(4)(6) during July 2008 to June 2009. This person was the Principal Investigator for Study GRC43, conducted October through December 2009, and one of four participating investigators overall. The applicant states that this amount was Honoraria/Fee for Service not directly related to the clinical trial. The applicant does not believe any bias, intentional or unintentional, was introduced by these financial arrangements in the conduct and evaluation of those clinical trials included in the submission. A FDA Form 3455 was submitted for this individual.

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 85 sites		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: no Significant equity interest held by investigator in sponsor of covered study: no		
Is an attachment provided with details of the disclosable financial interests/ arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

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

4.1 Chemistry, Manufacturing, and Controls

Review of the chemistry, manufacturing, and controls data submitted in this supplement was conducted by Dr. Vladimir Lugovtsev, OVRR/Division of Viral Products. The processes for manufacturing Fluzone Quadrivalent are the same as those of licensed Fluzone, except that an additional B strain is included at the formulation step, and no gelatin is added. The applicant provided data and validation reports for three consistency lots of Final Bulk and for Filled Final Containers, meeting all acceptance criteria.

4.2 Assay Validation

The applicant submitted a validation report, a validation protocol, and standard work instructions for their influenza virus hemagglutination inhibition (HAI) assay to this supplement. Statistical review of the validation report was conducted by Tielin Qin, OBE/Division of Biostatistics/Vaccine Evaluation Branch. In the validation report, intra- and inter-assay precision, accuracy, dilutability, specificity, and lower limit of quantitation were evaluated. Based on the acceptance criteria used, the performance of the HAI assay appears to be acceptable.

Of note, serum samples from Study GRC43 were initially tested by HAI at a commercial laboratory under the guidance of the applicant. In 2009, the applicant developed an optimized HAI assay ----------(b)(4)----------. Immunogenicity testing using the optimized assay was conducted by the applicant and was used in studies QIV03 and QIV04. GRC43 adult sera were re-tested under the modified conditions and these results were submitted to the supplement.

4.3 Nonclinical Pharmacology/Toxicology

Not applicable.

4.4 Clinical Pharmacology

Not applicable.

4.4.1 Mechanism of Action

Vaccination against influenza results in hemagglutination inhibition antibody titers. Specific levels of antibody have not been absolutely correlated with protection from influenza illness. In some studies, HI antibody titers of ≥ 1:40 have been associated with protection from influenza illness in up to 50% of subjects.

4.4.2 Human Pharmacodynamics (PD)

Not applicable

4.4.3 Human Pharmacokinetics (PK)

Not applicable

4.5 Statistical

Statistical review of the clinical data submitted in this supplement was conducted by Dr. Sang Ahnn, OBE/Division of Biostatistics/Vaccine Evaluation Branch. The focus of the review was on the two Phase 3 studies, QIV03 and QIV04. Based upon an independent examination of the submitted datasets, the reviewer concluded that the study objectives regarding immunogenic non-inferiority of Fluzone Quadrivalent compared to trivalent Fluzone were met, and noted no safety concerns. Please see Dr. Ahnn's review memorandum for details.

4.6 Pharmacovigilance

Review of the pharmacovigilance plan for Fluzone Quadrivalent was conducted by Dr. David Menschik, OBE/Division of Epidemiology/Vaccine Safety Branch. No postmarketing requirement was judged to be necessary.

As a postmarketing commitment, the applicant proposed the establishment of a pregnancy exposure registry. In this protocol, data regarding exposures of pregnant women to Fluzone Quadrivalent would be prospectively collected through spontaneous reporting from recipients or their health care providers. Baseline information would be collected at the time of reporting, and would be followed by a questionnaire submitted to the reporter to ascertain pregnancy and neonatal outcome. Contact information regarding this registry would be provided in the

Prescribing Information and Patient Information Sheet as well as on a company-sponsored website. The applicant may add further outreach to physicians through other media. Annual reports will be submitted with the Periodic Benefit-Risk Evaluation Report for Fluzone Quadrivalent, and a final study report will be submitted after the collection of six years of data. Based on a recent policy to improve the quality of data regarding the safety of vaccines recommended for pregnant women, CBER requested the applicant to establish instead a prospective cohort study with active recruitment of exposed and unexposed women, explaining that this design would conform more closely to the August 2002 *FDA Guidance to Industry: Establishing Pregnancy Exposure Registries*. Data collection would include patient interviews and medical record review, and the study would have pre-specified statistical power to rule out or detect differences in outcomes based on sample size. The applicant responded with some modifications to their protocol, including increasing the duration of the study to six years, but did not change the basic study design, maintaining that their planned methods were in accordance with the guidelines, and viewed the goal of their registry to be hypothesis generating rather than hypothesis testing. CBER accepted this response.

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

5.1 Review Strategy
This review focused on the results from two, Phase 3 clinical trials, QIV03 (randomized, single-blind trial in adults aged 65 years and older), and QIV04 (randomized, single-blind trial in children aged 6 months to less than 9 years), and one Phase 2 trial GRC43 (randomized, open-label trial in adults aged 18 years and older), Although the clinical endpoints used were similar across the studies, age-related differences in the reactogenicity and immunogenicity of inactivated influenza vaccines in general have been well described. Therefore, each trial was reviewed separately, and data from these studies were not pooled, either for the integrated summaries or for presentation in the package insert. No additional clinical studies were submitted in support of this supplement.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review
The clinical study reports, pertinent case report tabulations and forms (module 5), labeling (module 1.14), financial information (module 1.3.4), clinical overview (module 2.5), pediatric waiver request (module 1.9.1), and clinical summaries (module 2) were reviewed. In addition, amendments to the supplement (0284, 0287, 0294, 0304, 0308, 0309, 0310, 0311) were also reviewed.

5.3 Table of Clinical Trials
Table x lists the completed studies submitted to the supplement and included in the clinical review.

Table x. Clinical Studies Included in Supplemental BLA for Fluzone Quadrivalent

Study No. Country Start/End Date	**Study Description**	**Population**	**Treatment Assignment**	**Number of Subjects**
GRC43 Oct/Dec 2009	Phase 2, randomized, open-label, safety and immunogenicity, single dose	≥18 years	QIV TIV-1 TIV-2	190 190 190
QIV03 Oct/Dec 2010	Phase 3, randomized, observer-blind, safety and immunogenicity, single dose	≥65 years	QIV TIV-1 TIV-2	225 225 225

Study No. Country Start/End Date	Study Description	Population	Treatment Assignment	Number of Subjects
QIV04 Nov 2010/Jan 2012	Phase 3, randomized, observer-blind, safety and immunogenicity, one or two doses**	6 months - <9 years	QIV TIV-1 TIV-2	2902 736 725

Source: Adapted from sBLA 103914/5574; m 2.5 Clinical Overview
**Number of doses received according to ACIP recommendations

5.4 Consultations
There were no consultations for this product application.

5.4.1 Advisory Committee Meeting
There were no regulatory issues or concerns regarding this particular submission that necessitated advisory committee discussion. Previous VRBPAC meetings have discussed the need for a quadrivalent influenza vaccine.

5.4.2 External Consults/Collaborations
There were no external consults or collaborations for this application.

5.5 Literature Reviewed
Broder KR, Martin DB, Vellozzi C. In the heat of a signal: responding to a vaccine safety signal for febrile seizures after 2010-11 influenza vaccine in young children, United States. Vaccine. 2012 Mar 2;30(11):2032-4.

Castilla J, Godoy P, Domínguez A, et al. Influenza vaccine effectiveness in preventing out-patient, in-patient and severe cases of laboratory-confirmed influenza. Clin Infect Dis. 2013 Mar 26. [Epub ahead of print]

Centers for Disease Control and Prevention (CDC). Estimates of deaths associated with seasonal influenza --- United States, 1976-2007. MMWR Morb Mortal Wkly Rep. 2010 Aug 27;59(33):1057-62.

Fiore AE, Uyeki TM, Broder K, Finelli L, Euler GL, Singleton JA, Iskander JK, Wortley PM, Shay DK, Bresee JS, Cox NJ; Centers for Disease Control and Prevention (CDC). Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Recomm Rep. 2010 Aug 6;59(RR-8):1-62.

IOM (Institute of Medicine), 2012. Adverse effects of vaccines: evidence and causality. Washington, DC: The National Academies Press.

Leroy Z, Broder K, Menschik D, Shimabukuro T, Martin D. Febrile seizures after 2010-2011 influenza vaccine in young children, United States: a vaccine safety signal from the vaccine adverse event reporting system. Vaccine. 2012 Mar 2;30(11):2020-3.

Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis. 2012 Jan;12(1):36-44.

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.

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.

Talbot HK, Zhu Y, Chen Q, Williams JV, Thompson MG, Griffin MR. Effectiveness of Influenza Vaccine for Preventing Laboratory-Confirmed Influenza Hospitalizations in Adults, 2011-2012 Influenza Season. Clin Infect Dis. 2013 Apr 1.

Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, Cox NJ, Fukuda K. Influenza-associated hospitalizations in the United States. JAMA. 2004 Sep 15;292(11):1333-40.

Tse A, Tseng HF, Greene SK, Vellozzi C, Lee GM; VSD Rapid Cycle Analysis Influenza Working Group. Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010-2011. Vaccine. 2012 Mar 2;30(11):2024-31.

World Health Organization. (2009) Influenza (Seasonal). WHO Fact Sheet No. 211. accessed at: www.who.int/mediacentre/factsheets/fs211/en

6. DISCUSSION OF INDIVIDUAL CLINICAL TRIALS

6.1 Study GRC43

Title: Immunogenicity and Safety Among Children and Adults of the 2009-2010 Trivalent Influenza Vaccine, 2008-2009 Trivalent Influenza Vaccine, and Quadrivalent Influenza Vaccine (Intramuscular Route)

6.1.1 Objectives

Primary Objective

To describe the immunogenicity of the Quadrivalent Influenza Vaccine (QIV) compared with the 2009-2010 TIV and the 2008-2009 TIV among adults.

Secondary Objective

There were no secondary objectives.

Observational Objectives

To describe the safety and immunogenicity of:

- The 2009-2010 TIV vaccine among subjects ≥ 6 months to < 5 years, 18-60 years, and ≥ 61 years of age, and
- The 2008-2009 TIV and QIV vaccines among subjects 18-60 years and ≥ 61 years of age.

To evaluate the antibody response in terms of European Medicines Agency criteria for demonstration of immunogenicity (CHMP NfG CPMP/BWP/214/96).

> **Reviewer comment:** *The CHMP criteria are used for yearly evaluation of strain changes in influenza vaccines. These criteria do not address any U.S. regulatory objectives. These criteria differ from the criteria for the accelerated approval of trivalent inactivated seasonal influenza vaccines that are described in the FDA Guidance for Industry, "Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines" in the following ways:*

- *FDA criteria use two endpoints in the evaluation of a new vaccine: 1) seroconversion, defined as a four-fold or greater rise in HI antibody titers over baseline for all three vaccine antigens; and 2) the proportion of subjects with an HI antibody titer of at least 1:40 at three weeks following vaccination for each of the three vaccine antigens.*
- *FDA criteria use the lower bound of the 95% confidence interval, rather than the point estimate of the endpoints, to evaluate the target goal.*
- *FDA criteria require that all six endpoints (two endpoints for each of the three vaccine antigens) should be achieved.*

The pediatric component of this trial was conducted as part of an ongoing yearly study of Fluzone trivalent vaccine to support public health agencies in the selection and recommendation of antigen strains for influenza vaccines for the subsequent influenza season. Since the quadrivalent vaccine was not studied in the pediatric population in this study, the pediatric component will not be included in this review.

6.1.2 Design Overview

This trial was a randomized, open-label, active-controlled, multi-center, three-arm, Phase 2 trial of healthy subjects in three age strata (a 6-59 months age group, which will not be described in this review, and two age groups in adults: 18-60 years, and ≥61 years of age) to determine the immunogenicity and safety among children and adults of the 2009-10 TIV, 2008-09 TIV, and QIV. Subjects were randomized 1:1:1 to receive the 2009-10 TIV (Group 1), the 2008-09 TIV (Group 2) or QIV (Group 3).

Appropriate informed consent was obtained for each subject, and adult subjects were randomized by age stratum to one of three treatment arms. Each subject then underwent a medical history and blood draw for baseline HAI titers, after which the subject received one intramuscular dose of the assigned Fluzone vaccine. Blood was drawn 21 days after the final vaccination to assess the HAI response.

Table 1. Study GRC43 - Treatment Arms and Planned Enrollment by Age Group.

Study Group	18-60 years of age	≥61 years of age	Total
Group 1 (2009-10 TIV)	94	95	189
Group 2 (2008-09 TIV)	95	94	189
Group 3 (QIV)	95	95	190
Total	284	284	568

Source: Adapted from sBLA 103914/5574; Clinical Study Report GRC43 p58

Subjects received a single, 0.5 mL intramuscular dose of study vaccine on Day 0. Following completion of all study procedures on Day 21, subjects in Groups 2 and 3 were offered a dose of the licensed 2009-2010 TIV. All subjects were also offered a dose of monovalent A(H1N1) pandemic vaccine. Neither of these was considered a study vaccination, and no follow-up was conducted as part of this study.

6.1.3 Population

Inclusion Criteria

Subject is 18 years of age or older, in good health, willing to comply with the study procedures, and willing to give informed consent.

Exclusion Criteria

1. History of allergy to egg proteins, chicken proteins, or one of the constituents of the vaccine, such as thimerosal or formaldehyde.
2. History of serious adverse reaction to any influenza vaccine.
3. Laboratory-confirmed influenza infection or vaccination against influenza in the 6 months preceding enrollment in the study.
4. Prior personal history of Guillain-Barré syndrome.
5. Any vaccination scheduled between Day 0 and Day 21.
6. Participation in any other interventional drug or vaccine trial during participation in this study.
7. 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, including immunocompromising conditions, thrombocytopenia or bleeding disorder, and diabetes mellitus requiring pharmacological control.
8. Current use of alcohol or recreational drugs that may interfere with the subject's ability to comply with trial procedures.

Women of childbearing potential had to have a negative urine pregnancy test prior to vaccination and had to agree to use a reliable form of contraception. Women who were pregnant or breast feeding were excluded from study participation.

6.1.4 Study Treatments Mandated by the Protocol

Each 0.5 mL dose of study vaccine contains 15 µg of hemagglutinin from each of the influenza virus strains as outlined in Table 2:

Table 2. Study GRC43 – Vaccine Strains by Treatment Arm.

Vaccine Strain	QIV	2008-09 TIV	2009-10 TIV
A/Brisbane/59/2007, IVR148 (H1N1)	X	X	X
A/Uruguay/716/2007, NYMC X-175C (H3N2)*	X	X	X
B/Brisbane/60/2008	X		X
B/Florida/04/2006	X	X	

Source: Adapted from sBLA 103914/5574; Clinical Study Report GRC43, p. 64-66

All study vaccines were provided in single-dose (QIV) or multi-dose (2008-09 TIV and 2009-10 TIV) vials and were administered intramuscularly in the deltoid of choice.

QIV Fluzone vaccine is an egg-based, split antigen vaccine. Antibiotics are not used in the manufacture of the vaccine, and the vaccine did not contain preservatives. The QIV batch number used in this study was UD12581.

TIV Fluzone vaccine is also an-egg based, split antigen vaccine. Antibiotics were not used in the manufacture of the vaccines. In the Fluzone TIV formulation used in this study, thimerosal was included as a preservative. The 2009-2010 TIV batch number used in this study was U3190AA. The 2008-2009 TIV batch number used in this study was U2853AB.

6.1.5 Directions for Use

Not applicable.

6.1.6 Sites and Centers

This trial was conducted at four investigative sites in the United States and involved four investigators.

6.1.7 Surveillance/Monitoring

Immunogenicity

Immunogenicity was evaluated by measurement of serum hemagglutinin inhibition (HAI) titers on Day 0 and Day 21. For each vaccine strain, pre- and post-GMTs were calculated. HAI testing was initially conducted at ------(b)(4)------ under the guidance of Sanofi Pasteur.

Safety

Safety monitoring included the following:

- Twenty minute post-vaccination observation period
- Solicited adverse reactions following vaccination from Day 0 to Day 3
  - After vaccination, the subject was provided with a diary card, thermometer, and ruler
  - Solicited injection site adverse reactions included pain, erythema, swelling, induration, and ecchymosis; solicited systemic adverse reactions included fever, headache, malaise, myalgia, and shivering. These solicited reactions were graded for intensity using a scale of 1 to 3 provided with the diary card.
- Unsolicited adverse events.
  - Subjects were also instructed to record any unsolicited AEs that occurred from Day 0 to Day 21 on the diary card.
- Serious adverse events
  - Information on SAEs was collected and assessed throughout the trial from inclusion until Day 21.

Table 3. Study GRC43 – Schedule of Events

Visit Number	**Visit 1**	**Day 4 Telephone Contact**	**Visit 2**
Trial Timelines (Days)	Day 0	Day 4	Day 21
Time Windows (days)	-	4 days	21 to 28 days
Informed Consent	X		
Inclusion & Exclusion Criteria	X		
Medical History	X		
History- Directed Physical Examination	X		
Blood Sample (BS)†	X (BS1)		X (BS2)
Pregnancy Test (when applicable)	X		
Vaccination	X		
Diary Cards (DC) Provided	DC		
Diary Card Reminder		X‡	
Diary Cards Collected			DC
Unsolicited Adverse Events (including Serious Adverse Events)	To be reported throughout the trial		

Source: Adapted from sBLA 103914/5574; Clinical Study Report GRC34, p44.
† A blood sample, approximately 15 mL, was collected on Day 0 and Day 21.
‡ The subject was contacted by telephone on Day 4 to remind them to complete the diary card and to bring the diary card with them to Visit 2.

6.1.8 Endpoints and Criteria for Study Success

Immunogenicity

Primary Endpoint

Post-vaccination HAI antibody titer for the two influenza B virus strains

Secondary Endpoint

There were no secondary endpoints for immunogenicity

Observational Endpoints

Derived endpoints based on HAI antibody titers against the two influenza B strains:

- Ratio of individual post-vaccination/pre-vaccination titers
- Proportion with HAI titer ≥ 40 (1/dil) at pre-vaccination and post-vaccination
- Seroconversion: either a pre-vaccination titer < 10 (1/dil) and a postvaccination titer ≥ 40 (1/dil), or a pre-vaccination titer ≥ 10 (1/dil) and a ≥ 4-fold increase in post-vaccination titer.

Safety

Primary Endpoints

There were no primary endpoints for safety.

Secondary Endpoints

There were no secondary endpoints for safety.

Observational Endpoints

- Occurrence and intensity of solicited adverse events (ie, solicited injection site adverse reactions and solicited systemic adverse reactions) occurring within 3 days of vaccination,
- Occurrence and intensity of unsolicited AEs (including those occurring immediately within 20 minutes of vaccination) occurring between Day 0 and 21..
- Occurrence and intensity of SAEs occurring from Day 0 to 21.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Subjects were randomized in a 1:1:1 ratio to the three vaccine arms. Vaccine assignment was centralized using computer-generated randomization. The study was conducted in an open-label design.

Primary Analysis

Non-inferiority of QIV compared to 2009-2010 TIV was to be demonstrated if the lower limit of the two-sided 95% confidence interval of the ratio of GMT_{QIV} / $GMT_{2009\text{-}2010\ TIV}$ as > 2/3 for strain B1. Non-inferiority of QIV compared to 2008-2009 TIV was to be demonstrated if the lower limit of the two-sided 95% confidence interval of the ratio of GMT_{QIV} / $GMT_{2008\text{-}2009\ TIV}$ was > 2/3 for strain B2. Primary analyses were performed on the per-protocol analysis set, while observational analyses were performed on the full analysis set.

Observational Analyses

Safety

Safety data were analyzed using descriptive statistics.

Immunogenicity

The following immunogenicity measures, each with 95% confidence intervals, were calculated for each of the strains.

- Geometric mean of anti-HAI assay titers pre-vaccination (Day 0) and post-vaccination (Day 21).
- Mean geometric increase: Geometric mean titer fold rise of individual post-vaccination/pre-vaccination titers.
- The percentage of subjects with a titer ≥40 (1/dil) pre-vaccination and post-vaccination.
- Seroconversion rate: Percentage 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.

Immunogenicity results for adult subjects in each age stratum (18-60 years, ≥61 years) were compared with European requirements for yearly evaluation of influenza vaccines (CHMP NfG CPMP/BWP/214/96). For each vaccine strain and age stratum, the recommendations are to meet at least one of the three CHMP criteria defined in Table x.

Table 4. Study GRC43 - Immunogenicity Criteria for Seasonal Influenza Vaccines Defined by CHMP

	18-60 years	**≥61 years**
Seroconversion rate*	>40%	>30%
Mean geometric increase†	>2.5	>2.0
Percentage of subjects with HI titers ≥ 1:40‡	>70%	>60%

Source: Adapted from sBLA 103914/5574; Clinical Study Report GRC43, Table 1.1 p54
* Percentage of subjects with either a pre-vaccination titer < 10 (1/dilution [1/dil]) and a post-vaccination titer ≥ 40 (1/dil) or a pre-vaccination titer ≥10 (1/dil) and a ≥ -fold increase in post-vaccination titer.
† Geometric mean of individual ratios (post-/pre-vaccination titers).

> **Reviewer comment:** *As noted above, these criteria are not used by FDA and their description here does not imply endorsement.*

Additional exploratory non-inferiority comparisons of the GMTs for QIV to the GMTs of the pooled TIV group (i.e., subjects vaccinated with either 2009-2010 TIV or 2008-2009 TIV) were performed for strain A/Brisbane/59/2007 (A/H1N1) and strain A/Uruguay/716/2007 (A/H3N2).

Study Results

6.1.10 Study Population and Disposition

The study was conducted at 4 sites in the United States. The study began on 01 October 2009 and completed on 22 December 2009.

6.1.10.1 Populations Enrolled/Analyzed

Three analysis sets were used: the Per-Protocol Analysis Set (PP), the Full Analysis Set (FAS), and the Safety Analysis Set (SAS). The PP analysis included all subjects who met eligibility criteria; received the study vaccine within the specified time intervals; provided pre- and post-vaccination serum specimens within the specified time intervals; and had at least one post-vaccination serological result. The FAS included all subjects who received at least one dose of study vaccine and had a valid post-vaccination serology result. The Safety Analysis Set was defined as those subjects who received the study vaccine. SAS analyses were conducted according to the vaccine received rather than according to the randomization. Immunogenicity analyses were performed on the PP Analysis Set and confirmed on the FAS. Safety analyses were performed on the SAS.

6.1.10.1.1 Demographics

Table 5 summarizes the subject demographic and baseline characteristics. In general, the proportions of these factors were comparable among the three vaccination groups, and this balance was preserved in the FAS and PP analysis cohorts (not shown).

Table 5: Study GRC43 - Demographic and Baseline Characteristics According to Randomized Vaccine Group - Adult Groups - All Randomized

		2009-2010 TIV	2008-2009 TIV	QIV	Total
Demographic		**(N=190)**	**(N=190)**	**(N=190)**	**(N=570)**
Sex					
Male	n (%)	61 (32.1)	66 (34.7)	60 (31.6)	187 (32.8)
Female	n (%)	129 (67.9)	124 (65.3)	130 (68.4)	383 (67.2)
Age (years)					
	Median	61.0	60.8	61.6	61.0
	Range	[20.0; 88.1]	[18.7; 87.2]	[18.0; 89.7]	[18.0; 89.7]
Race*					
White	n (%)	165 (86.8)	166 (87.4)	173 (91.1)	504 (88.4)
Black	n (%)	23 (12.1)	19 (10.0)	13 (6.8)	55 (9.6)

*Individual race categories, other than White or Black, were reported at rates of <2%.
Source: Adapted from sBLA 103914/5574; Clinical Study Report GRC43 Table 9.10, p 193

When comparing the two age groups, 18-60 years and ≥61 years, the older age group had a lower proportion of females (61.5% vs. 72.9%) and was less racially diverse compared to the younger age group (94.1% vs. 82.7% White). These differences occurred to a similar degree among the three treatment groups.

> **Reviewer comment:** *Although the gender and racial and ethnic distribution of the study population does not reflect the distribution of the U.S. population, antibody responses to influenza immunization have not been correlated to gender, race, or ethnicity; therefore, the results are relevant to the U.S. population.*

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Not applicable

6.1.10.1.3 Subject Disposition
Subject disposition is summarized in Table 6. Four (0.7%) subjects in the safety analysis set were excluded from the full analysis set for the following reasons: did not provide a post-vaccination blood sample (2009-2010 TIV, two [1.1%] subjects; and 2008-2009 TIV, one [0.5%] subject) and subject's post-vaccination blood sample did not produce a valid serological result (2009-2010 TIV, one [0.5%] subject). One subject (2008-2009 TIV group) in the full analysis set was excluded from the per-protocol analysis set because the subject was vaccinated with H1N1 vaccine prior to the Visit 2 blood draw. The distribution of protocol deviations in the subset of subjects 18-60 years of age was generally similar to that of subjects ≥ 61 years of age

Table 6: Study GRC43 - Summary of Subject Disposition According to Randomized Vaccine Groups - Adult Groups

	2009-2010 TIV	2008-2009 TIV	QIV	Total
Disposition	**n (%)**	**n (%)**	**n (%)**	**n (%)**
All Randomized (N)	**190 (100.0)**	**190 (100.0)**	**190 (100.0)**	**570 (100.0)**
Randomized but did not receive any vaccination	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Safety analysis set	**190 (100.0)**	**190 (100.0)**	**190 (100.0)**	**570 (100.0)**
Full analysis set	**187 (98.4)**	**189 (99.5)**	**190 (100.0)**	**566 (99.3)**
In the safety analysis set but excluded from the full analysis set	3 (1.6)	1 (0.5)	0 (0.0)	4 (0.7)
Did not provide a post-vaccination blood sample	2 (1.1)	1 (0.5)	0 (0.0)	3 (0.5)
Subject's post-vaccination blood sample did not produce a valid serological result	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Per-protocol (PP) analysis set*	**187 (98.4)**	**188 (98.9)**	**190 100.0)**	**565 (99.1)**
In the full analysis set but excluded from the per-protocol analysis set (received a protocol prohibited therapy/medication/vaccine)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)
Subjects completing the study	**190 (100.0)**	**190 (100.0)**	**190 (100.0)**	**570 (100.0)**

Source: Adapted from sBLA 103914/5574; Clinical Study Report GRC43, Table 9.201, p788
*Subjects with more than one deviation to the per-protocol are counted only once and are classified in the category of deviation listed first in this table.

> **Reviewer comment:** *The number of subjects excluded from the Per-Protocol analysis population was small, suggesting that the study was appropriately conducted with adequate subject follow-up.*

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

The primary objective of the study was to describe the antibody response to the influenza B antigens contained in the QIV, the 2009-2010 TIV and the 2008-2009 TIV among adults as assessed by GMT ratios. For each comparison, non-inferiority was demonstrated if the lower limit of the two-sided 95% CI of the GMT ratio was >2/3. The results of the primary endpoint analysis are presented in Table 7.

Table 7: Study GRC43 - Comparison of GMTs Against B/Brisbane/60/2008 (B1) and B/Florida/04/2006 (B2) After QIV With Those After 2009-2010 TIV and 2008-2009 TIV - Per-Protocol Analysis Set

	QIV N=190	2009-2010 TIV N=187	2008-2009 TIV N=188		Non-Inferiority Criteria Met
Antigen Strain	**GMT (95% CI)**	**GMT (95% CI)**	**GMT (95% CI)**	**GMT Ratio (95% CI)**	
B/Brisbane/60/2008(B1)	101 (85.6, 120)	114 (97.8, 134)	--	0.89 (0.70, 1.12)	Yes
B/Florida/04/2006(B2)	155 (133, 180)	--	135 (117, 156)	1.15 (0.93, 1.42)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report GRC43, Table 9.225, p846

An additional non-inferiority comparison described the immunogenicity of QIV compared with pooled TIV group (either the 2009-2010 TIV or the 2008-2009 TIV) among adults as assessed by GMT ratios for each of the two influenza A virus strains separately among subjects. As above, non-inferiority was demonstrated if the lower limit of the two-sided 95% CI of the GMT ratio was >2/3. The results of this analysis are presented in Table 8.

Table 8: Study GRC43 - Comparison of GMTs Against A/Brisbane/59/2007(H1N1) and A/Uruguay/716/2007(H3N2) After QIV With Those After 2009-2010 TIV and 2008-2009 TIV - Per-Protocol Analysis Set

	QIV N=190	Pooled TIV N=375		Non-Inferiority Criteria Met
Antigen Strain	**GMT (95% CI)**	**GMT (95% CI)**	**GMT Ratio (95% CI)**	
A/Brisbane/59/2007(A/H1N1)	161 (137, 189)	151 (134, 171)	1.06 (0.87, 1.31)	Yes
A/Uruguay/716/2007(A/H3N2)	304 (249, 370)	339 (293, 392)	0.90 (0.70, 1.15)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report GRC43, Table 9.226, p847

> **Reviewer comment**: *Although the study was designed only to describe immunogenicity, criteria for determination of non-inferiority were included in the statistical analysis plan. The antibody response to both influenza A antigens and both influenza B antigens after vaccination with QIV was non-inferior to the antibody response after vaccination with TIV. These results suggest a lack of interference with antibody response when an additional influenza B subtype was added to the vaccine.*

6.1.11.2 Analyses of Observational Endpoints

The first observational objective of the study was to describe GMTs, GMTRs, seroconversion rates, and proportion with titers ≥ 1:40 post-vaccination induced by QIV and the two TIVs by age stratum, as shown in Table 9. *The second observational objective* was to evaluate immunogenicity, of the 2009-2010 TIV, 2008-2009 TIV, and prototype QIV vaccines in subjects 18-60 years of age and subjects ≥61 years of age, using CHMP immunogenicity criteria for seasonal influenza vaccines.

Table 9: Study GRC43 - Summary of HAI Antibody Responses for Each Strain – Per-Protocol Analysis Set

Antigen Strain		2009-10 TIV 18-60y (N=94)	2009-10 TIV ≥65y (N=93)	2009-10 TIV Overall (N=187)	2008-09 TIV 18-60y (N=94)	2008-09 TIV ≥65y (N=94)	2008-09 TIV Overall (N=188)	QIV 18-60y (N=93)	QIV ≥65y (N=96)	QIV Overall (N=190)
A/Brisbane/59/2007 (A/H1N1)	Pre-Vaccination GMT	28.5	26.4	27.5	28.8	28.1	28.4	36.6	21.0	27.6
	Post-Vaccination GMT	250	84.5	145	254	97.6	157	221	118	161
	GMT ratio (post/pre)	7.56	2.85	4.64	7.32	3.23	4.88	5.23	5.04	5.14
	Seroconversion rate	68.8%	41.9%	55.4%	62.8%	40.9%	51.9%	59.6%	58.3%	58.9%
	Post-Vaccination Proportion with Titers ≥ 1:40	95.7%	84.0%	89.8%	98.9%	85.1%	92.0%	96.8%	88.5%	92.6%
A/Uruguay/716/2007 (A/H3N2)	Pre-Vaccination GMT	25.8	34.7	29.9	26.6	40.4	32.7	30.8	47.9	38.5
	Post-Vaccination GMT	431	213	302	511	282	380	301	306	304
	GMT ratio (post/pre)	14.0	5.19	8.52	14.9	6.37	9.75	7.60	5.70	6.57
	Seroconversion rate	78.5%	61.3%	69.9%	74.5%	53.8%	64.2%	67.0%	58.3%	62.6%
	Post-Vaccination Proportion with Titers ≥ 1:40	96.8%	95.7%	96.3%	94.7%	93.6%	94.1%	95.7%	93.8%	94.7%
B/Brisbane/60/2008(B1)	Pre-Vaccination GMT	19.6	24.8	22.0	--	--	--	21.5	18.3	19.9
	Post-Vaccination GMT	159	82.4	114	--	--	--	132	78.3	101
	GMT ratio (post/pre)	6.79	2.79	4.35	--	--	--	5.16	3.41	4.19
	Seroconversion rate	71.0%	40.9%	55.9%	--	--	--	59.6%	46.9%	53.2%
	Post-Vaccination Proportion with Titers ≥ 1:40	95.7%	84.0%	89.8%	--	--	--	89.4%	81.3%	85.3%
B/Florida/04/2006(B2)	Pre-Vaccination GMT	--	--	--	28.5	37.3	32.6	31.1	23.6	27.1
	Post-Vaccination GMT	--	--	--	179	101	135	210	115	155
	GMT ratio (post/pre)	--	--	--	5.47	2.61	3.78	6.02	4.13	4.98
	Seroconversion rate	--	--	--	55.3%	33.3%	44.4%	59.6%	56.3%	57.9%
	Post-Vaccination Proportion with Titers ≥ 1:40	--	--	--	96.8%	88.3%	92.6%	94.7%	89.6%	92.1%

Source: Adapted from sBLA 103914/5574; Clinical Study Report GRC43,Table 9.207 p797-798, and Table 9.208 and 9.209, p799-801
[1] GMT ratio is the geometric mean of the individual post-vaccination/pre-vaccination titer ratios [2] Seroconversion is defined as either a pre-vaccination HAI titer < 1:10 and a post-vaccination titer ≥1:40 or a pre-vaccination titer ≥1:10 and a four-fold increase in post-vaccination

Reviewer comment: *As shown in Table 9, immune responses as measured by multiple parameters were similar after vaccination with QIV as with either TIV. Of note, immune responses were lower in the older age cohort. This is expected, and is likely due to immunosenescence.*

6.1.11.3 Subpopulation Analyses
See above for analyses stratified by age group. Analyses by gender and race/ethnicity revealed no significant differences in immunogenicity (see statistical review).

6.1.11.4 Dropouts and/or Discontinuations
Analyses using the Final Analysis Set demonstrated essentially the same results.

6.1.11.5 Exploratory and Post Hoc Analyses
Not applicable.

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 the study or control vaccine. Analyses were conducted according to the vaccine received rather than according to the randomization. All 570 subjects aged ≥18 years who were enrolled in the study received the assigned vaccine and were included in the SAS. As noted above, this was a non-blinded study.

6.1.12.2 Overview of Adverse Events
The incidence of solicited injection site and systemic adverse reactions were similar in all three treatment arms, occurring in 44.2%-53.2% and 28.9%-38.4% of subjects, respectively. Unsolicited adverse events occurred in 17.9%-24.7% of subjects and were generally mild in nature, while unsolicited adverse reactions occurred in 5.3%-6.8% of subjects and were mostly local in nature. No unexpected safety events were reported.

Solicited Adverse Reactions

Solicited injection site adverse reactions within 3 days after vaccine injection were reported by 101 (53.2%) subjects in the 2009-2010 TIV group, 84 (44.2%) subjects in the 2008-2009 TIV group, and 91 (47.9%) subjects in the QIV group. The most frequently reported solicited injection site adverse reaction was pain (see Table x). One Grade 3 reaction (pain at the injection site) was reported by one subject each in the 2009-2010 TIV and QIV groups. The frequencies of subjects with pain were higher for subjects 18-60 years of age than for subjects ≥ 61 years of age. The intensity, time of onset, and number of days of occurrence of solicited injection site adverse reactions were generally similar between the age groups.

Solicited systemic adverse reactions after vaccine injection were reported by 73 (38.4%) subjects in the 2009-2010 TIV group, 55 (28.9%) subjects in the 2008-2009 TIV group, and 64 (33.7%) subjects in the QIV group. The most frequently reported solicited systemic adverse reactions were myalgia, headache, and malaise (see Table x). Grade 3 reactions were reported for headache (one subject each for 2009-2010 TIV and QIV) and for malaise (two subjects for 2009-2010 TIV, one subject for 2008-2009 TIV, and two subjects for QIV). Solicited systemic adverse reactions typically started within 2 days after vaccination and typically lasted for 1 or 2 days after onset. The frequency of subjects with myalgia, headache, and malaise were generally higher for subjects 18-60 years of age than for subjects ≥61 years of age. The intensity, time of onset, and number of days of occurrence of solicited systemic adverse reactions were generally similar between the age groups.

Table 10 presents the incidence of solicited local and general adverse reactions reported within 3 days (Day 0 to 3) following vaccination.

Table 10: Study GRC43 - Solicited Injection Site and Systemic Adverse Reactions after Vaccine Injection, by Maximum Intensity during Solicited Period - Safety Analysis Set

Subjects with at least one:	**2009-2010 TIV (N=190)**	**2008-2009 TIV (N=190)**	**QIV (N=190)**
	n (%)	n (%)	n (%)
Pain	99 (52.1)	82 (43.2)	90 (47.4)
Grade 3	1 (0.5)	0 (0.0)	1 (0.5)
Erythema	3 (1.6)	3 (1.6)	2 (1.1)
Swelling	6 (3.2)	2 (1.1)	1 (0.5)
Induration	3 (1.6)	1 (0.5)	1 (0.5)
Ecchymosis	1 (0.5)	1 (0.5)	1 (0.5)
Fever	1 (0.5)	1 (0.5)	0 (0.0)
Headache	35 (18.4)	34 (18.0)	30 (15.8)
Grade 3	1 (0.5)	0 (0.0)	1 (0.5)
Malaise	29 (14.7)	23 (12.1)	20 (10.5)
Grade 3	2 (1.1)	1 (0.5)	2 (1.1)
Myalgia	48 (25.3)	32 (16.8)	45 (23.7)
Shivering	10 (5.3)	6 (3.2)	5 (2.6)

Source: Adapted from sBLA 103914/5574; Clinical Study Report GRC43, Table 9.68 p295 and Table 9.56 p264
Note: Grade 3 events are listed for those specific adverse reactions for which at least one case of that severity was reported.

> **Reviewer comment:** *The incidence of subjects with any solicited adverse reactions and of each solicited adverse reaction was similar for both TIV arms and the QIV arm. Grade 3 adverse reactions were uncommon. Overall, rates of individual solicited adverse reactions were lower than those reported in the current Fluzone package insert.*

Unsolicited Adverse Events

There were no immediate (within 20 minutes after vaccination) unsolicited AEs in any vaccine group.

Unsolicited AEs within 21 days after vaccine injection were reported by

- 23.7% (45/190) of subjects in the 2009-2010 TIV group,
- 23.7% (45/190) of subjects in the 2008-2009 TIV group, and
- 17.4% (33/190) of subjects in the QIV group.

The most commonly reported unsolicited non-serious AEs were headache, cough, and oropharyngeal pain. The percentage of subjects with each of these adverse events was similar between the three study arms with the greatest difference between arms for headaches (5.3% in each TIV arm and 2.6% in QIV arm). No individual AE was reported in 6% or more of subjects.

Overall, the frequencies of adult subjects 18-60 years of age who reported at least one unsolicited non-serious adverse event were higher than in subjects ≥ 61 years of age in the 2009-2010 TIV and QIV groups, but lower in the 2008-2009 TIV group.

> **Reviewer comment:** *Unsolicited adverse events occurred at similar rates among the treatment arms. The nature and incidence of individual adverse events were generally typical for this population.*

Unsolicited Adverse Reactions

Unsolicited adverse reactions (i.e., AEs judged by the investigator to be related to vaccination) within 21 days after vaccine injection were reported by

- 12 (6.3%) subjects in the 2009-2010 TIV group,
- 13 (6.8%) subjects in the 2008-2009 TIV group, and
- 10 (5.3%) subjects in the QIV group.

The most common AEs reported as vaccine-related in all groups were oropharyngeal pain and cough. Overall, the frequencies of adult subjects 18-60 years of age who reported at least one unsolicited AR were higher than in subjects ≥ 61 years of age in the 2009-2010 TIV and QIV groups, but lower in the 2008-2009 TIV group.

> **Reviewer comment:** *Unsolicited adverse reactions were defined as AEs determined to be related to vaccination by the study investigators, but these attributions were not individually evaluated by the reviewer. Overall, these events occurred with similar frequencies across arms. and there was no increase in any system organ class or individual adverse reaction.*

6.1.12.3 Deaths

There were no deaths reported in this study.

6.1.12.4 Nonfatal Serious Adverse Events

Two subjects experienced nonfatal SAEs. Both were considered by the investigator to be unrelated to study vaccine:

- A 67 year old male (2008-2009 TIV group) developed gastrointestinal bleeding 26 days after vaccination. The subject had a past medical history significant for diverticulosis, hypertension, stroke, and GI surgery (colectomy for bleeding in 2007, normal colonoscopy one year prior), and presented with a rectal bleeding. He was hospitalized for observation and discharged the next day.
- A 38 year old female (QIV group) experienced benign paroxysmal positional vertigo and unspecified chest pain 12 days after vaccination. The subject had a past medical history significant for gestational diabetes, hysterectomy, cholecystectomy, tonsillectomy, and pelvic laparoscopy. The patient was hospitalized for evaluation of initial symptoms and

discharged the following day. The chest pain resolved one day after onset, the vertigo was ongoing.

Reviewer comment: *The narratives for these two SAEs were reviewed. The reviewer concurs with the investigators' assessments. There was no increase in serious adverse events in the QIV arm compared to the TIV arms.*

6.1.12.5 Adverse Events of Special Interest (AESI)
There was no surveillance for AESIs in this trial.

6.1.12.6 Clinical Test Results
There were no clinical laboratory evaluations in this trial.

6.1.12.7 Dropouts and/or Discontinuations
There were no discontinuations due to adverse events in any vaccine group.

6.2 Study QIV03
Title: Safety and Immunogenicity Trial Among Adults Administered Quadrivalent Influenza Vaccine

6.2.1 Objectives
Primary Objective

To demonstrate non-inferiority of antibody responses to QIV compared with licensed 2010-2011 TIV (containing the influenza B/Victoria strain included in QIV) and investigational TIV (containing the influenza B/Yamagata strain included in QIV) as assessed by geometric mean titer ratios for each of the four virus strains separately among subjects ≥65 years of age.

Secondary Objective

There were no secondary objectives.

Observational Objectives

Immunogenicity
Non-inferiority
To demonstrate non-inferiority of antibody responses to QIV compared with licensed 2010-2011 TIV (containing the primary B strain) and investigational TIV (containing the alternate B strain) as assessed by seroconversion rates separately among subjects ≥65 years of age.

Superiority

To demonstrate superiority of antibody responses 21 days post-vaccination to each B strain in QIV compared with the TIV that does not contain the corresponding B strain, as assessed by geometric meant titer ratios and seroconversion rates among subjects ≥65 years of age.

Descriptive

To describe geometric meant titers, geometric meant titer ratios, seroconversion rates, and proportion of titers ≥1:40 induced by QIV and TIV.

Safety

To describe the safety profile of QIV among subjects 18 years of age and older, as assessed by solicited injection site and systemic AEs collected for 7 days post- vaccination, unsolicited AEs collected for 21 days post-vaccination, and AEs of special interest (AESIs) and SAEs collected for 21 days post-vaccination.

Serum Collection
To submit remaining available sera from subjects given the licensed 2010-2011 TIV to the Center for Biologics Evaluation and Research (CBER) for further analysis by the World Health Organization (WHO), the CDC, and the FDA to support selection and recommendation of strains for subsequent years' influenza vaccines.

Reviewer note: *The last objective regarding serum collection will not be reviewed.*

6.2.2 Design Overview
This was a Phase 3, four-arm, active-controlled, observer-blind, multi-center trial to determine the immunogenicity and safety of the QIV, licensed 2010-11 TIV (containing the influenza B/Victoria strain included in QIV) and an investigational TIV (containing the influenza B/Victoria strain included in QIV) among adults ≥ 65 years of age assigned to one of three arms. A fourth group of subjects aged 18 to <65 years were enrolled in an open-label cohort as part of an annual influenza vaccine study in healthy adults to document the safety and immunogenicity of the licensed seasonal TIV vaccine, and are not further discussed.

After a medical history and initial blood draw for baseline HAI titers, subjects ≥ 65 years of age were randomized at a ratio of 1:1:1 to receive one intramuscular dose of their assigned vaccine during Visit 1 (Day 0). All subjects were followed up for approximately 21 days post-vaccination. Blood was drawn 21 days post- vaccination to determine the HAI response. Safety data collection included immediate surveillance for 20 minutes post-vaccination; solicited AE information for 7 days post-vaccination; unsolicited AE information and AESIs and SAE information from Day 0 to Day 21.

6.2.3 Population
Inclusion Criteria

The study enrolled subjects who were 18 years of age and older (≥65 years of age for Groups 1-3), were able to provide informed consent, and were able to comply with study procedures. For a woman of childbearing potential, use of an effective method of contraception or abstinence from at least 4 weeks prior to the first vaccination until at least 4 weeks post- vaccination.

Exclusion Criteria
A potential subject meeting <u>any</u> of the following criteria was ineligible for trial enrollment:

1. History of serious adverse reaction to any influenza vaccine.
2. Receipt of any influenza vaccine since 01 August 2010 (including 2009 H1N1 monovalent vaccine).
3. Known systemic hypersensitivity or allergy to egg proteins, latex, or to any of the vaccine components, or history of a life-threatening reaction to the vaccine(s) used in the trial or to a vaccine containing any of the same substances.
4. History of Guillain-Barré syndrome (GBS).
5. Receipt of blood or blood-derived products in the past 3 months.
6. 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 including (but not limited to): thrombocytopenia; bleeding disorder; immunodeficiency; known

seropositivity for human immunodeficiency virus (HIV), hepatitis B, or hepatitis C; or current alcohol or drug use.
7. Receipt of any vaccine in the 4 weeks preceding the trial vaccination or planned receipt of any vaccine between Day 0 and Day 21.
8. Participation in another interventional clinical trial investigating a vaccine, drug, medical device, or medical procedure in the 4 weeks preceding the first study vaccination or during the course of the study.
9. Identified as employees of the Investigator or study center, with direct involvement in the proposed study or other studies under the direction of that Investigator or study center, as well as family members (i.e. husband, wife and their children, adopted or natural) of the employees or the Investigator.

6.2.4 Study Treatments Mandated by the Protocol

Subjects in Groups 1-3 were randomized 1:1:1 to receive one of the following vaccines:

- QIV, single dose, No Preservative (investigational product)
- Licensed 2010-2011 TIV, No Preservative (Fluzone®) (control product)
- Investigational TIV with alternate B strain (control product)

Each 0.5 mL dose of vaccine contained 15 µg hemagglutinin from each of its component vaccine strains, as outlined in Table 11:

Table 11. Study QIV03 – Vaccine Strains by Treatment Arm

Vaccine Strain	QIV	Licensed TIV 2010-11	Investigational TIV
A/California/07/2009 (H1N1)	X	X	X
A/Victoria/210/2009 (H3N2)	X	X	X
B/Brisbane/60/2008 (B1)	X	X	
B/Florida/04/2006 (B2)	X		X

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV03, p. 50-53.

Quadrivalent inactivated influenza vaccine and trivalent influenza vaccines are egg-based, split antigen vaccines. Antibiotics are not used in the manufacture of the vaccine.
All study vaccines were provided in pre-filled syringes and administered intramuscularly in the deltoid of choice.

The QIV batch number used in this study was UD14439. The licensed 2010-2011 TIV batch number used in this study was UD14453. The investigational TIV batch number used in this study was UD14445.

Additionally, following completion of all study procedures on Day 21, all subjects $\geq$ 65 years were offered a dose of the licensed 2010-2011 TIV. This was not considered a study vaccination.

6.2.5 Directions for Use

Not applicable

6.2.6 Sites and Centers

This trial was conducted at 12 investigative sites in the United States and involved 12 investigators.

6.2.7 Surveillance/Monitoring

Immunogenicity

Immunogenicity was evaluated by measurement of serum hemagglutinin inhibition (HAI) titers on Day 0 and Day 21. For each vaccine strain, pre- and post-GMTs were calculated. Assays were performed by Sanofi Pasteur.

Safety

- Subjects were kept under observation for 20 minutes after vaccination. Any AE observed during this period was recorded as a solicited (onset recorded as Day 0) or unsolicited (onset recorded as immediate) AE.
- After vaccination, subjects were provided with a safety diary card, a digital thermometer, and a flexible ruler, and were instructed on how to record solicited adverse reactions pre-listed in the diary card, including injection site adverse reactions (pain, erythema, and swelling) and systemic adverse reactions (fever, headache, malaise, and myalgia), and any other unsolicited medical adverse events that occurred from Day 0 to Day 7.
- Subjects were contacted by telephone 8 days after vaccination to remind them to record all safety information in the diary card.
- At Visit 2 (Day 21), a directed examination was performed, if indicated based on interim history, and the subject was asked about any solicited adverse reactions and unsolicited AEs recorded in the diary card, as well as about any other AEs that may have occurred since Visit 1. Each unsolicited systemic AE was assessed as either not related or related to vaccination.
- Information on SAEs and adverse events of special interest (AESIs) was collected and assessed throughout the trial, from inclusion to Day 21. AESIs included new onset of Guillain-Barré syndrome (GBS), Bell's palsy, encephalitis/myelitis, optic neuritis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, and were analyzed as SAEs.
- AEs likely related to the product were followed by the Investigator until resolution or stabilization.

Table 12. Study QIV03 - Schedule of Events.

Visit/Contact	**Visit 1**	**Visit 2**
Trial Timelines (Days)	Day 0	Day 21
Time Windows (Days)	NA	21 to 28 days
Informed Consent	X	
Collection of Vital Signs	X[a]	
Significant Medical History	X	
History-Directed Physical Examination	X	
Urine Pregnancy Test (when applicable)	X	
Blood Sampling (BL)[b]	BL1	BL2
Vaccination	X	
Immediate Surveillance (20 min)	X	
Diary Card (DC) Provided	X	
Diary Card Reviewed and Collected		X
Termination Record		X
Collection of Adverse Events of Special Interest	To be reported throughout the study period	To be reported throughout the study period
Serious Adverse Events		

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV03, p45
a. Vital signs were recorded prior to vaccination on Day 0 and again before leaving the study clinic post-vaccination. Vital signs included temperature, pulse, respiratory rate, and blood pressure.
b. A blood sample, approximately 15 mL, was collected on Day 0 and Day 21.

6.2.8 Endpoints and Criteria for Study Success

Primary Endpoint

The endpoints for the primary objective were the HAI geometric mean titers (GMT) for each of the four virus strains at 21 days post-vaccination.

Secondary Endpoint

There were no secondary endpoints.

Observational Endpoints

Immunogenicity

Non-inferiority

The endpoint for the non-inferiority observational objective was the seroconversion rate, defined as the percentage of subjects with either a pre-vaccination titer <10 (1/dil) and post-vaccination titer ≥ 40 (1/dil), or a pre-vaccination titer ≥10 (1/dil) and a ≥4-fold increase in post-vaccination titer for each of the four virus strains at 21 days post-vaccination.

Superiority

The endpoints for the superiority observational objectives were the GMT and seroconversion rates, as defined above, for the two influenza B virus strains at 21 days post-vaccination.

Descriptive

Immunogenicity was evaluated in all subjects prior to vaccination on Day 0 and Day 21 using HAI. The following immunogenicity parameters were calculated for each vaccine and each influenza strain with 95% CIs:

- Geometric mean HAI assay titers pre-vaccination (Day 0) and post-vaccination (Day 21).
- Geometric means of the individual titer ratios of post-vaccination/pre-vaccination.
- The percentages of subjects with titer ≥ 40 (1/dil) pre-vaccination and post-vaccination.
- Seroconversion rates: as defined above.

Safety

The observational endpoints for the evaluation of safety were:

1. Unsolicited systemic AEs reported in the 20 minutes after vaccination.
2. Solicited injection site adverse reactions occurring between Day 0 and Day 7
3. Solicited systemic adverse reactions occurring between Day 0 and Day 21
4. Unsolicited AEs and SAEs from Day 0 to21.

6.2.9 Statistical Considerations & Statistical Analysis Plan

The study was performed in an observer-blinded fashion:

- Unblinded qualified study staff who were not involved with safety evaluation and other trial procedures prepared and administered the vaccine.
- Blinded Investigators and study staff who conducted safety assessments did not know which vaccine was administered.
- Subjects did not know which vaccine was administered.

Subjects were randomized in a 1:1:1 ratio to one of the three study arms using an IVRS system.

Primary Analysis

Non-inferiority was demonstrated if the lower limit of the two-sided 95% CI of the ratio of the GMTs (QIV divided by TIV) on Day 21 was >0.66 for each of the four virus strains separately among subjects ≥ 65 years of age. Data from the two TIVs were pooled together for each of the

A strains. Comparisons for the B strains were done between QIV and TIV with the corresponding B strain.

Observational Analyses

Immunogenicity

Non-inferiority

Non-inferiority was demonstrated if the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (QIV minus TIV) on Day 21 was >-10% for each of the four virus strains separately among subjects. Data from the two TIVs were pooled together for each of the A strains. Comparisons for the B strains were done between QIV and TIV with the corresponding B strain. For each strain, 95% CI of the difference in seroconversion rates between QIV and TIV was calculated using the exact binomial distribution (Clopper-Pearson method).

Immunologic Superiority

GMTs: Superiority was demonstrated if the lower limit of the two-sided 95% CI of the ratio of the GMTs (QIV divided by TIV) was >1.5 for each B strain in QIV compared with the corresponding B strain not contained in each TIV.

Seroconversion: Superiority was demonstrated if the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (QIV minus TIV) was >10% for each B strain in QIV compared with the corresponding B strain not contained in each TIV.

Safety

Safety data were analyzed using descriptive statistics.

Study Results

The study was conducted at 12 sites in the United States. The study began on 08 October 2010 and the active phase was completed on 22 December 2010.

6.2.10 Study Population and Disposition

Overall, a total of 739 subjects were randomized in Study QIV03, and 735 (99.5%) subjects completed the study. Of these, 675 subjects were healthy adults ≥65 years of age were enrolled (225 in each vaccine group).

6.2.10.1 Populations Enrolled/Analyzed

Three analysis sets were used: the Per-Protocol Analysis Set (PP), the Full Analysis Set (FAS), and the Safety Analysis Set (SAS). Criteria for these analysis sets were the same as those described in Section 6.1.10.1.

6.2.10.1.1 Demographics

Table 13 summarizes the subject demographic and baseline characteristics. In general, the proportions of these factors were comparable among the three vaccination groups, and this balance was preserved in the FAS and PP analysis cohorts (not shown).

Table 13: Study QIV-03 - Demographics and Baseline Characteristics According to Randomized Vaccine Groups - ≥65 years – All Randomized.

Demographic Attribute		**QIV (N=225)**	**2010-2011 TIV (N=225)**	**Investigational TIV (N=225)**	**Total (N=675)**
Sex					
Male	n (%)	96 (42.7)	99 (44.0)	104 (46.2)	299 (44.3)
Female	n (%)	129 (57.3)	126 (56.0)	121 (53.8)	376 (55.7)
Age (Years)					
	Median	71.1	71.9	71.6	71.6
	Range	[65.1,92.2]	[65.0,94.6]	[65.1,92.3]	[65.0,94.6]
Race/Ethnic origin*					
White	n (%)	197 (87.6)	202 (89.8)	205 (91.1)	604 (89.5)
Black	n (%)	9 (4.0)	4 (1.8)	2 (0.9)	15 (2.2)
Hispanic	n (%)	19 (8.4)	17 (7.6)	14 (6.2)	50 (7.4)

*Individual race/ethnicity categories other than White, Black, and Hispanic were reported at rates of <2%
Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV03, Table 9.4 p147

Reviewer comment: As with Study GRC43, the gender and racial and ethnic distribution of the study population in QIV03 does not reflect the distribution of the U.S. population. But again, antibody responses to influenza immunization have not been correlated with gender, race, or ethnicity; therefore, the results should be relevant to the U.S. population.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Not applicable

6.2.10.1.3 Subject Disposition
A total of 675 subjects 65 years of age or older were enrolled, randomized, and vaccinated in the study. Of these subjects, 15 subjects (QIV, 5 [2.2%] subjects; 2010-2011 TIV, 6 [2.7%] subjects; and investigational TIV, 4 [1.8%] subjects) had one or more protocol violations, including failure to provide a post-vaccination sample (3 subjects), failure to produce a valid serological result (5 subjects), and failure to provide a sample within the proper time window (7 subjects), and were therefore excluded from the FAS and/or PP analysis sets, as described in Table 14.

Table 14: Study QIV03 - Subject Disposition According to Randomized Vaccine Groups - ≥65 Years of Age – All Randomized

Disposition	QIV n (%)	2010-11 TIV n (%)	Investigational TIV n (%)	Total n (%)
All randomized	225 (100.0)	225 (100.0)	225 (100.0)	675 (100.0)
Safety Analysis Set	**225 (100.0)**	**225 (100.0)**	**225 (100.0)**	**675 (100.0)**
Full Analysis Set	**223 (99.1)**	**220 (97.8)**	**224 (99.6)**	**667 (98.8)**
Did not provide a post-vaccination blood sample	1 (0.4)	2 (0.9)	0 (0.0)	3 (0.4)
Did not produce a valid serological result	1 (0.4)	3 (1.3)	1 (0.4)	5 (0.7)
Per-Protocol Analysis Set	**220 (97.8)**	**219 (97.3)**	**221 (98.2)**	**660 (97.8)**
Provided sample out of the proper time window	3 (1.3)	1 (0.4)	3 (1.3)	7 (1.0)
Subjects completing the study	**224 (99.6)**	**223 (99.1)**	**225 (100.0)**	**672 (99.6)**
Did not complete study due to:	1 (0.4)	2 (0.9)	0 (0.0)	3 (0.4)
SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other AE	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Non-compliance	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Lost to follow-up	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV03, Table 9.3 p145-6

> **Reviewer comment:** *All subjects who were randomized in the study were also vaccinated and included in the Safety Analysis Set. The majority of subjects (97.8%) were also included in the Per Protocol Analysis Set. This suggests that the study was well conducted with adequate subject follow-up.*

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoints

The primary objective of the study was to demonstrate non-inferiority of antibody responses to QIV compared with licensed 2010-2011 TIV (containing a B/Victoria strain) and an Investigational TIV (containing a B/Yamagata strain) as assessed by GMT ratios for each of the four virus strains separately among subjects ≥ 65 years of age. For each comparison, non-inferiority was demonstrated if the lower limit of the two-sided 95% CI of the GMT ratio was >0.66. The results of the primary endpoint analysis are presented in Tables 15 and 16.

Table 15: Study QIV03 - Comparison of Geometric Mean Titers (GMTs) against Influenza A Strains after QIV with GMTs after TIV - ≥65 Years - Per-Protocol Analysis Set

	QIV N=220	Pooled TIV N=440		Non-Inferiority Criteria Met
Antigen Strain	**GMT (95% CI)**	**GMT (95% CI)**	**Ratio of GMT (95% CI)**	
A/California/07/2009 (A/H1N1)	231 (188, 283)	270 (234, 311)	0.85 (0.67, 1.09)	Yes
A/Victoria/210/2009 (A/H3N2)	501 (422, 593)	324 (285, 367)	1.55 (1.25, 1.92)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV03, Table 9.41, p257

Table 16: Study QIV03 - Comparison of Geometric Mean Titers (GMTs) against Influenza B Strains after QIV with GMTs after TIV with Corresponding B Strain - ≥65 Years - Per-Protocol Analysis Set

	QIV N=220	2010-2011 TIV N=219	Investigational TIV N=221		Non-Inferiority Criteria Met
Antigen Strain	**GMT (95% CI)**	**GMT (95% CI)**	**GMT (95% CI)**	**Ratio of GMT (95% CI)**	
B/Brisbane/60/2008(B1)	73.8 (63.0, 85.3)	57.9 (50.6, 66.4)	--	1.27 (1.05, 1.55)	Yes
B/Florida/04/2006(B2)	61.1 (52.5, 71.2)	--	54.8 (47.5, 63.3)	1.11 (0.90, 1.37)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV03, Table 9.42, p258

As shown in these tables, the antibody response after vaccination with Fluzone QIV was non-inferior to the antibody response after vaccination with the trivalent Fluzone formulations for both influenza A strains and both influenza B strains.

> **Reviewer comment:** *The primary objective of the study, to demonstrate immunologic non-inferiority of the antibody response to all four influenza antigens in QIV compared to the corresponding antigens in two TIV formulations, was met.*

6.2.11.2 Analyses of Observational Endpoints

There were no secondary objectives or endpoints; however, the results for observational objectives were provided.

Non-Inferiority by Seroconversion

The first observational objective of the study was to demonstrate non-inferiority of the antibody responses to QIV compared with licensed 2010-2011 TIV (containing the primary B strain) and investigational TIV (containing the alternate B strain) as assessed by seroconversion rates separately among subjects ≥ 65 years of age. For each comparison, non-inferiority was demonstrated if the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (QIV minus TIV) was > -10%. The results of this observational endpoint analysis are presented in Tables 17 and 18.

Table 17: Study QIV03 - Comparison of Seroconversion Rates against Influenza A Strains after QIV with those after TIV - ≥ 65 Years - Per-Protocol Analysis Set

	QIV N=220	Pooled TIV N=440		Non-Inferiority Criteria Met
Antigen Strain	**n (%) [95% CI]**	**n (%) [95% CI]**	**Difference in SCR (95% CI)**	
A/California/07/2009 (A/H1N1)	145 (65.9) [59.2, 72.2]	307 (69.8) [65.3, 74.0]	-3.9 (-11.5, 3.6)	No
A/Victoria/210/2009 (A/H3N2)	152 (69.1) [62.5, 75.1]	261 (59.3) [54.6, 64.0]	9.8 (1.96, 17.2)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV03, Table 9.43, p259
n is the number of subjects with a seroconversion
SCR = seroconversion rate

Table 18: Study QIV03 - Comparison of Seroconversion Rates against Influenza B Strains after QIV with those after TIV with Corresponding B strain - ≥ 65 Years - Per-Protocol Analysis Set

	QIV N=220	2010-2011 TIV N=219	Investigational TIV N=221		Non-Inferiority Criteria Met
Antigen Strain	**n (%) [95% CI]**	**n (%) [95% CI]**	**n (%) [95% CI]**	**Difference in SCR (95% CI)**	
B/Brisbane/60/2008(B1)	63 (28.6) [22.8, 35.1]	41 (18.7) [13.8, 24.5]	--	9.91 (1.96, 17.7)	Yes
B/Florida/04/2006(B2)	73 (33.2) [27.0, 39.8]	--	69 (31.2) [25.2, 37.8]	1.96 (-6.7, 10.6)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV03, Table 9.44 p260
n is the number of subjects with a seroconversion
SCR = seroconversion rate

Non-inferiority criteria were met for only 3 of 4 seroconversion endpoints, as the lower bound for the confidence interval of the difference in rates was below acceptance criteria for the A/H1N1 strain.

> **Reviewer comment:** *This endpoint for demonstration of non-inferiority using seroconversion rates was only marginally missed (lower bound 95% CI of -11.5 with criteria for demonstration of non-inferiority of -10%), the endpoint was observational only, and the criteria were met for the other three antigens. In addition, the result for this endpoint may be related to a higher prevalence of seropositivity in this age group against this strain at baseline. Consistent with this observation, the proportion of subjects with a final titer ≥1:40 was 91%. Finally, the primary endpoint, which was the GMT ratio for this strain, did meet criteria. Therefore, these results do not raise significant concerns regarding the immunogenicity of QIV in this age group.*

Superiority Analyses by GMT Ratio and Seroconversion

The second observational objective was to demonstrate superiority of antibody responses 21 days post-vaccination to each influenza B strain in QIV compared with the TIV that does not contain the corresponding B strain, as assessed by the ratio of GMTs and seroconversion rates among subjects ≥ 65 years of age. For the GMT comparison, superiority was demonstrated if the lower

limit of the two-sided 95% CI of the ratio of the GMTs was > 1.5. The results of the GMT observational endpoint analysis are presented in Table 19.

Table 19: Study QIV03 - Comparison of Geometric Mean Titers (GMTs) against Influenza B Strains after QIV with these after TIV without Corresponding B Strain (Cross-Reactive Antibody) - ≥65 Years - Per-Protocol Analysis Set.

	QIV N=220	2010-2011 TIV N=219	Investigational TIV N=221		Superiority Criteria Met
Antigen Strain	**GMT (95% CI)**	**GMT (95% CI)**	**GMT (95% CI)**	**Ratio of GMT (95% CI)**	
B/Brisbane/60/2008(B1)	73.8 (63.9, 85.3)	--	42.2 (36.5, 48.7)	1.75 (1.43, 2.14)	No
B/Florida/04/2006(B2)	61.1 (52.5, 71.2)	28.5 (24.6, 33.0)	--	2.14 (1.74, 2.65)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV03, Table 9.45 p261

The criteria for superiority were met for the influenza B/Florida/04/2006 strain but not for the influenza B strain of the other lineage.

> **Reviewer comment:** *Only one of two success criteria was met for this observational objective. However, the point estimate for the GMT ratio was 1.75, with the lower bound missing the pre-specified criterion only marginally, and the superiority criteria for this strain were met using the differences in seroconversion rates.*

The third observational objective was to demonstrate superiority of antibody responses 21 days post-vaccination to each influenza B strain in QIV compared to the TIV that does not contain the corresponding B strain, as assessed by seroconversion rates among subjects ≥ 65 years of age. Superiority was demonstrated if the lower limit of the two-sided 95% CI of the difference of the seroconversion rates was >10% for each B strain in QIV compared with the corresponding B strain not contained in each TIV. The results of this observational endpoint analysis are presented in Table 20.

Table 20: Study QIV03 - Comparison of Seroconversion Rates against Influenza B Strains after QIV with these after TIV without Corresponding B Strain (Cross-Reactive Antibody) - >= 65 Years - Per-Protocol Analysis Set

	QIV N=220	2010-2011 TIV N=219	Investigational TIV N=221		Superiority Criteria Met
Antigen Strain	**n (%) [95% CI]**	**n (%) [95% CI]**	**n (%) [95% CI]**	**Difference in SCR (95% CI)**	
B/Brisbane/60/2008(B1)	63 (28.64) [22.76, 35.10]	--	19 (8.60) [5.26, 13.10]	20.04 (12.9, 27.0)	Yes
B/Florida/04/2006(B2)	73 (33.18) [27.00, 39.83]	20 (9.13) [5.67, 13.75]	--	24.05 (16.6, 31.2)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV03, Table 9.46 p262
n is the number of subjects with a seroconversion
SCR = seroconversion rate

Superiority criteria were met for each of the influenza B strains.

> **Reviewer comment:** *Although the superiority criteria were not met for the influenza B/Brisbane subtype on analyses using the comparison of GMTs, superiority criteria were met on the analysis using the comparison of seroconversion rates, in which SCR estimates were more than 20% higher in the QIV group compared to the TIV groups without the corresponding influenza B strain.*

Descriptive Analyses

The last observational objective was to describe GMTs, GMT ratios, seroconversion rates, and proportion of subjects with titer ≥1:40 induced by QIV and the two TIVs. The results of these analyses are presented in Table 21.

Table 21: Study QIV03 - Summary of HAI Antibody Responses for Each Influenza Strain - ≥65 Years – Per-Protocol Analysis Set

Antigen Strain		QIV N=220	2010-2011 TIV N=219	Investigational TIV N=221
A/California/07/2009 (A/H1N1)	Pre-Vaccination GMT	21.7	24.8	21.1
	Post-Vaccination GMT	231	269	271
	GMT ratio[1] (post/pre)	8.81	9.18	10.6
	Seroconversion rate [2]	65.9%	66.7%	72.9%
	Post-Vaccination Proportion ≥ 1:40	91.4%	91.3%	91.9%
A/Victoria/210/2009 (A/H3N2)	Pre-Vaccination GMT	52.3	48.3	42.3
	Post-Vaccination GMT	501	291	360
	GMT ratio (post/pre)	8.72	5.65	7.73
	Seroconversion rate	69.1%	55.7%	62.9%
	Post-Vaccination Proportion ≥ 1:40	100.0%	95.4%	95.9%
B/Brisbane/60/2008(B1)	Pre-Vaccination GMT	27.1	29.0	28.5
	Post-Vaccination GMT	73.8	57.9	42.2
	GMT ratio (post/pre)	2.46	1.83	1.34
	Seroconversion rate	28.6%	18.7%	8.6%
	Post-Vaccination Proportion ≥ 1:40	77.7%	71.7%	60.2%
B/Florida/04/2006(B2)	Pre-Vaccination GMT	20.2	18.7	19.7
	Post-Vaccination GMT	61.1	28.5	54.8
	GMT ratio (post/pre)	2.65	1.40	2.47
	Seroconversion rate	33.2%	9.1%	31.2%
	Post-Vaccination Proportion ≥ 1:40	73.2%	46.1%	67.4%

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV03, Table 9.36 p241-244
[1] GMT ratio is the geometric mean of the individual post-vaccination/pre-vaccination titer ratios
[2] Seroconversion is defined as either a pre-vaccination HAI titer < 1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥ 1:10 and a four-fold increase in post-vaccination

Reviewer comment: *Although the FDA criteria for demonstration of immunogenicity (FDA Guidance for Industry, "Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines.") are intended for the approval of seasonal trivalent influenza vaccines, the results for seroconversion rates and for percentage of subjects with post-vaccination HAI titers ≥1:40 met the criteria for all influenza strains included in the QIV and TIV vaccines.*

6.2.11.3 Subpopulation Analyses
Analyses of immunogenicity results by the CBER statistical reviewer revealed no significant differences by race/ethnicity or gender.

6.2.11.4 Dropouts and/or Discontinuations
The immunogenicity analysis was performed on the Per Protocol population, and the number of subjects excluded from the Per Protocol population was low (N=9) and did not affect the outcome.

6.2.11.5 Exploratory and Post Hoc Analyses
Not applicable

6.2.12 Safety Analyses
6.2.12.1 Methods
All safety analyses were conducted with the Safety Analysis Set, which included all subjects who received the study or control vaccine. Analyses were conducted according to the vaccine received rather than according to the randomization. All 675 subjects aged ≥65 years enrolled in the study received the assigned vaccine and were included in the SAS.

6.2.12.2 Overview of Adverse Events
The incidence and intensity of solicited injection site and systemic adverse reactions were similar in all three treatment arms, occurring in 24.1%-33.5% and 20.9%-24.6% of subjects, respectively. Unsolicited adverse events occurred in 10.2%-12.4% of subjects and were generally mild in nature (Grade 3 in 0.9%-1.8%), while unsolicited adverse reactions occurred in 1.8%-2.7% of subjects and were mostly local in nature. No unexpected safety events were reported.

Solicited Adverse Reactions

Solicited injection site adverse reactions after vaccine injection were reported by 33.5% (75/224) of subjects in the QIV group, 29.5% (66/224) of subjects in the 2010-2011 TIV group, and 24.0% (54/225) of subjects in the investigational TIV group.

Solicited systemic adverse reactions after vaccine injection were reported by 24.6% (55/224) of subjects in the QIV group, 24.1% (54/224) of subjects in the 2010-2011 TIV group, and 20.9% (47/225) of subjects in the investigational TIV group.

Table 22 presents the incidence of solicited local and general adverse events reported within 7 days (Day 0 to 7) following vaccination.

Table 22: Study QIV03 - Solicited Injection Site and Systemic Adverse Reactions after Vaccine Injection, by Maximum Intensity during the Solicited Period - ≥ 65 Years - Safety Analysis Set

	QIV (N=224)	2010-2011 TIV (N=224)	Investigational TIV (N=224)
Subjects with at least one:	n (%)	n (%)	n (%)
Pain	73 (32.6)	64 (28.6)	52 (23.1)
Grade 3	2 (0.9)	0 (0.0)	0 (0.0)
Erythema	6 (2.7)	3 (1.3)	3 (1.3)
Swelling	4 (1.8)	3 (1.3)	0 (0.0)
Fever	3 (1.3)	0 (0.0)	2 (0.9)
Grade 3	1 (0.4)	0 (0.0)	1 (0.4)
Headache	30 (13.4)	26 (11.6)	26 (11.6)
Grade 3	1 (0.4)	0 (0.0)	1 (0.4)
Malaise	24 (10.7)	14 (6.3)	26 (11.6)
Grade 3	1 (0.4)	0 (0.0)	2 (0.9)
Myalgia	41 (18.3)	41 (18.3)	32 (14.2)
Grade 3	1 (0.4)	0 (0.0)	1 (0.4)

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV03, Table 9.22 p183 and Table 9.26 p187

> **Reviewer Comment:** *Slightly higher rates of solicited local AEs were observed in the QIV arm, mostly due to Grade 1 pain. This may be due to the higher antigen content contained in QIV compared to TIV. However, there was no increase in Grade 3 pain nor any increase in the rate of systemic AEs.*

Unsolicited Adverse Events

There were no immediate (within 20 minutes after vaccination) unsolicited AEs in any vaccine group.

Unsolicited AEs within 21 days after vaccine injection were reported by

- 12.4% (28/225) of subjects in the QIV group,
- 10.7% (24/225) of subjects in the 2010-2011 TIV group, and
- 10.2% (23/225) of subjects in the investigational TIV group.

No individual unsolicited adverse event was reported in 2% or more of subjects. The most commonly reported unsolicited non-serious AEs were oropharyngeal pain (8 (1.2%)), and rhinorrhea, injection site induration, and headache (5 (0.74%) each). Grade 3 unsolicited non-serious AEs were reported in 6 (0.9%) subjects.

Reviewer comment: There was no increase in the total percentage or the percentage of subjects with individual unsolicited AEs in the QIV arm compared to the TIV arms.

Unsolicited Adverse Reactions

Unsolicited adverse reactions (i.e., AEs judged by the investigator to be related to vaccination) within 21 days after vaccine injection were reported by

- 2.7% (6/225) of subjects in the QIV group (4 injection site, 2 systemic)
- 2.7% (6/225) of subjects in the 2010-2011 TIV group (6 injection site, 1 systemic), and
- 1.8% (4/225) of subjects in the investigational TIV group (3 injection site, 1 systemic).

Unsolicited systemic ARs included diarrhea, nasopharyngitis, cough, and postnasal drip. None of the unsolicited ARs were Grade 3 or higher in intensity.

> **Reviewer comment:** *There was no increase in AEs judged as vaccine-related in the QIV arm compared to the TIV arms. As in Study GRC43, the assessment of an adverse event as an adverse reaction was made by the investigators. These determinations were not individually evaluated by the reviewer.*

6.2.12.3 Deaths
There were no deaths reported in this study.

6.2.12.4 Nonfatal Serious Adverse Events
Three subjects experienced nonfatal SAEs. All were considered by the investigator to be unrelated to study vaccine:

- A 72 year old male (2010-2011 TIV group) who developed partial detached retina of the left eye 16 days after vaccination.
- A 75 year old female (2010-2011 TIV group) who developed right hand cellulitis due to a cat bite wound, admitted to hospital 9 days after vaccination.
- A 66 year old female (Investigational TIV group) who was diagnosed with malignant melanoma of the left lower leg 7 days after vaccination.

> **Reviewer comment:** *The narratives for these three SAEs were reviewed. The reviewer concurs with the investigator assessments.*

6.2.12.5 Adverse Events of Special Interest (AESI)
There were no reported cases of AESIs in this trial.

6.2.12.6 Clinical Test Results
There were no clinical laboratory evaluations in this trial.

6.2.12.7 Dropouts and/or Discontinuations
One subject, a 73.6 year old male (2010-2011 TIV group) experienced 2 AEs (pruritis and diarrhea) on the day of vaccination that led to study discontinuation. The AEs were considered by the Investigator to be related to study vaccine.

6.3 Study QIV04
Title: Safety and Immunogenicity Among Children Administered Quadrivalent Influenza Vaccine

6.3.1 Objectives
Primary Objective

To demonstrate non-inferiority of antibody responses to quadrivalent influenza vaccine (QIV) compared with licensed 2010-2011 trivalent influenza vaccine (TIV) (containing the influenza B/Victoria strain included in QIV) and investigational TIV (containing the influenza B/Yamagata strain included in QIV) as assessed by geometric mean titer ratios and seroconversion rates after the final vaccination separately within two age groups (6 to <36 months and 3 to <9 years of age) and overall (6 months to <9 years).

Secondary Objective

To demonstrate superiority of antibody responses to each influenza B strain in QIV compared with antibody titers following vaccination with the TIV that does not contain the corresponding B strain, as assessed by geometric mean titer ratios and seroconversion rates.

Observational Objectives

Immunogenicity
- To describe the proportion of subjects with post-vaccination HAI titers ≥ 1:40 induced by QIV among subjects 6 months to <9 years of age compared with those of TIV
- To describe geometric mean titers, geometric mean titer ratios, seroconversion rates, and the proportion of subjects with titers ≥ 1:40 induced by QIV and TIV among children requiring 1 dose and among children requiring 2 doses

Safety
To describe the safety profile of QIV among subjects 6 months to <9 years of age, as assessed by solicited injection site and systemic adverse reactions collected for 7 days after each vaccination, unsolicited adverse events (AE)s collected from Day 0 to Day 28 (or Day 0 to Day 56 for those subjects requiring 2 doses) and events of special interest and SAEs collected from Day 0 through 6 months following the final vaccination.

Serum Collection
To submit remaining available sera from a subset of subjects given the licensed 2010-2011 TIV to the Center for Biologics Evaluation and Research (CBER) for further analysis by the World Health Organization (WHO), the CDC, and the Food and Drug Administration (FDA) to support selection and recommendation of strains for subsequent years' influenza vaccines.

Reviewer note: *The last objective regarding serum collection will not be reviewed.*

6.3.2 Design Overview
QIV04 was a Phase 3, randomized, observer-blinded, active-controlled, 3-arm multi-center trial to demonstrate the non-inferiority of antibody responses to QIV compared to licensed 2010-2011 TIV (containing the influenza B/Victoria strain included in QIV) and an investigational TIV containing an influenza B strain (containing the influenza B/Yamagata strain included in QIV) among children in two age strata (ages 6 months to <36 months and 3 years to <9 years). Enrollment was stratified by age group at each site to achieve approximately a proportion of 50% in each age group for the study overall.

After enrollment and randomization in an approximately 4:1:1 ratio to the QIV, licensed TIV, and Investigational TIV treatment arms, all subjects received their assigned influenza vaccine on Day 0. For subjects requiring 2 doses of influenza vaccine according to ACIP guidance, a second dose of the assigned vaccine was given on Day 28. Blood specimens were obtained from all subjects at baseline and 28 days after the final vaccination and assayed for immunogenicity. Solicited adverse reactions were monitored for 7 days after each vaccination, unsolicited AEs were monitored betweenDay 0 and Day 28 (for 1-dose series) or Day 0 and Day 56 (for 2-dose series), and AESIs and SAEs were monitored from Day 0 through 6 months following the final vaccination.

6.3.3 Population

Inclusion Criteria

A potential subject had to meet the following criteria to be considered for trial enrollment:

1. Subject was 6 months to < 9 years of age on the day of inclusion. Subject was healthy, and for subjects 6 months to < 24 months of age, born at full term of pregnancy (≥ 37 weeks) and with a birth weight ≥ 2.5 kg
2. Parent/guardian was willing to comply with the study procedures and to grant informed consent.

Exclusion Criteria

A potential subject meeting <u>any</u> of the following criteria was ineligible for trial enrollment:

1. History of allergy to egg proteins, latex, or any constituents of the vaccine
2. History of serious adverse reaction to any influenza vaccine
3. Receipt of any influenza vaccine since 01 August 2010 (including 2009 H1N1 monovalent vaccine)
4. History of Guillain-Barré syndrome (GBS)
5. Any vaccination, including routine childhood vaccines, scheduled between Day 0 and Day 28 (or Day 0 and Day 56 for those requiring 2 doses)
6. Receipt of any vaccine in the 4 weeks preceding the first study vaccination
7. Participation in another interventional clinical trial in the 4 weeks preceding the first study vaccination or during the course of the study
8. 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 including bleeding disorder, immunodeficiency, developmental delay, neurologic disorder, seizure disorder, or known seropositivity for human immunodeficiency virus (HIV), hepatitis B, or hepatitis C
9. Immediate family history of congenital immune deficiency
10. Employees of the Investigator or study center, with direct involvement in the proposed study or other studies under the direction of that Investigator or study center, as well as family members of the employees or the Investigator

6.3.4 Study Treatments Mandated by the Protocol

Subjects were randomized to receive one of the following vaccines:

- QIV, single dose, No Preservative (investigational product)
- Licensed 2010-2011 TIV, TIV, No Preservative (Fluzone), (containing the influenza B/Victoria strain recommended for the 2010-2011 influenza season [B1]) (control product)
- Investigational TIV (containing the influenza B/Yamagata strain recommended in previous seasons [B2]) (control product)

Each 0.25 mL dose of vaccine contains 7.5 µg hemagglutinin and each 0.5 mL dose of vaccine contained 15 µg hemagglutinin from each of its component vaccine strains, as outlined in Table 23:

Table 23. Study QIV04 – Vaccine Strains by Treatment Arm

Vaccine Strain	QIV	Licensed TIV 2010-11	Investigational TIV
A/California/07/2009 (H1N1)	X	X	X
A/Victoria/210/2009 (H3N2)	X	X	X
B/Brisbane/60/2008 (B1)	X	X	
B/Florida/04/2006 (B2)	X		X

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, p.60-64

Quadrivalent inactivated influenza vaccine and trivalent influenza vaccines are egg-based, split antigen vaccines. Neither antibiotics nor preservatives were used in the manufacture of the vaccine.

All study vaccines were provided in pre-filled syringes (0.25 mL and 0.5 mL single-dose) and administered intramuscularly in the anterolateral muscle of the thigh or deltoid, as appropriate. Study vaccines were administered on Day 0 as a single 0.25-mL dose (for subjects 6 months to < 36 months of age) or a single 0.5-mL dose (for subjects 3 years to < 9 years of age). For subjects requiring 2 doses per ACIP recommendations, a second dose of the same vaccine at the same volume as the first dose was administered at Day 28.

The QIV batch numbers used in this study were UD14442 (0.25 mL) and UD14439 (0.5 mL). The licensed 2010-2011 TIV batch numbers used in this study were UT3576DA (0.25 mL), UD14453 (0.5 mL), and U3641BA (replacement for UT3576DA). The investigational TIV batch numbers used in this study were UD14448 (0.25 mL), UD14445 (0.5 mL), UD14674 (replacement for UD14448), and UD14675 (replacement for UD14445).

Additionally, following completion of all study procedures, subjects were offered a dose of licensed 2010-2011 TIV, through 30 June 2011 (expiration date of the vaccine). This was not considered a study vaccination.

6.3.5 Directions for Use
Not applicable.

6.3.6 Sites and Centers
This trial was conducted at 69 investigative sites in the United States (US).

6.3.7 Surveillance/Monitoring
Immunogenicity
Immunogenicity was evaluated by measurement of serum hemagglutinin inhibition (HAI) titers pre-vaccination on Day 0 and post-vaccination, 28 days after the final dose. For each vaccine strain, pre- and post-GMTs were calculated. Assays were performed by Sanofi Pasteur.

Safety
- Subjects were kept under observation for 20 minutes after vaccination. Any AE observed during this period was recorded as a solicited (onset recorded as Day 0) or unsolicited (onset recorded as immediate) AE.
- After vaccination, the subject's parent/guardian was provided with a safety diary card, a digital thermometer, and a ruler, and instructed on how to record solicited adverse reactions

  - Parents/guardians were to measure body temperature once per day, preferably at the same time of day (optimally, the evening), and also at the time of any apparent fever. The highest observed daily temperature and route of measurement were to be recorded in the diary card for later entry in the eCRF. The preferred route was rectal for subjects 6 yo <=23 months, and oral/axillary for subjects 24 months of age or older.
- Solicited injection site and systemic adverse reactions differed by age, as summarized in Table 24:

Table 24. Study QIV04 – Solicited Adverse Reactions by Age Group

	6 months through 23 months	**24 months through <9 years**
Solicited injection site adverse reactions	Tenderness Erythema Swelling	Pain Erythema Swelling
Solicited systemic adverse reactions	Fever Vomiting Abnormal crying Drowsiness Loss of appetite Irritability	Fever Headache Malaise Myalgia

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Tables 3.2-3.5, p. 74-77

- Subjects were contacted by telephone 8 days after vaccination to remind them to record all safety information in the diary card.
- At the Day 28 visit, a directed examination was performed, if indicated based on interim history, and the subject or parent/guardian was asked about any solicited adverse reactions and unsolicited AEs recorded in the diary card, as well as about any other AEs that may have occurred since Day 0.
- A memory aid was provided on Day 28 for subjects who received a single vaccination and on Day 56 for subjects who received two vaccinations.
  - All SAEs were followed from Day 0 through 6 months.
  - AESIs were analyzed as SAEs, and included new onset of Guillain-Barré syndrome (GBS), Bell's palsy, encephalitis/myelitis, optic neuritis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and febrile seizures reported from Day 0 through 6 months following the final vaccination.

Table 25: Study QIV04 – Study Procedures for Subjects Requiring 2 Visits (1 Vaccination)

Visit Number	Visit 1	Visit 2
Trial Timelines (Days)	Day 0	Day 28
Time Windows (Days)	--	+ 28-35 days
Informed Consent/Assent	X	
Collection of Vital Signs	X[a]	
Medical History	X	
Physical Examination	X[b]	X[b]
Blood Sampling (BL)[c]	BL1	BL2
Vaccination[d]	X	
Immediate Surveillance (20 min)	X	
Diary Card (DC) Provided	DC1	
Diary Card Collected		DC1
6 month memory aid provided		X
Termination Record		X
Collection of AESIs and SAEs	X	X

Table 26: Study QIV04 – Study Procedures for Subjects Requiring 3 Visits (2 Vaccinations)

Visit Number	Visit 1	Visit 2	Visit 3
Trial Timelines (Days)	Day 0	Day 28	Day 56
Time Windows (Days)	--	+ 28-35 days	+ 28-35 days
Informed Consent/Assent	X		
Collection of Vital Signs	X[a]	X[a]	
Medical History	X		
Physical Examination	X[b]	X[b]	X[b]
Blood Sampling (BL)[c]	BL1		BL2
Vaccination[d]	X	X	
Immediate Surveillance (20 min)	X	X	
Diary Card (DC) Provided	DC1	DC2	
Diary Card Collected		DC1	DC2
Review of Influenza Vaccination History[e]		X	
6 month memory aid provided			X
Termination Record			X
Collection of AESIs and SAEs	X	X	X

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, p55
a. Vital signs were recorded again before leaving the study clinic post-vaccination. Vital signs included temperature, pulse, respiratory rate, and blood pressure.
b. A comprehensive physical assessment was conducted on Day 0. A history-directed physical examination was conducted at Day 28 and Day 56.
c. A blood sample, approximately 5 mL, was collected at Day 0, prior to vaccination and Day 1 (for subjects receiving 1 vaccination) or at Day 0, prior to vaccination and Day 56 (for subjects receiving 2 vaccinations).
d. One or 2 doses of influenza vaccine were administered according to ACIP guidance in effect during the study. If 2 doses of influenza vaccine were indicated, 1 dose was administered during Day 0 and the second dose administered approximately 28 days later, during Visit 2.
e. Influenza vaccination history was reviewed through IVRS to confirm eligibility of subjects to receive 2nd dose.

6.3.8 Endpoints and Criteria for Study Success

Primary Endpoints

The endpoints for the primary objective were:

- Geometric mean titers: The HAI GMTs (for each of the 4 virus strains) at 28 days after the final vaccination
- Seroconversion 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 days after the final vaccination

Secondary Endpoints
The endpoints for the secondary objective were the HAI GMTs and seroconversion rates for each influenza B strain measured 28 days after the last dose.

Observational Endpoints

Immunogenicity
The endpoints for the observational immunogenicity objectives were the HAI GMTs, GMT ratios, seroconversion rates, and percentage of subjects with post-vaccination HAI titers ≥ 1:40 induced by QIV compared with those of TIV

Safety
The endpoints for the observational safety objectives were:
- Unsolicited systemic AEs reported in the 20 minutes after vaccination.
- Injection site adverse reactions and solicited systemic adverse reactions occurring between Day 0 and Day 7 after vaccination.
- Unsolicited AEs between Day 0 and Day 28 (or between Day 0 and Day 56 for those subjects requiring 2 doses) including:
    - All unsolicited adverse events, followed for 28 days post-vaccination for subjects receiving a single dose of study vaccine and for 56 days for subjects receiving two doses of study vaccine
    - SAEs, AESIs, and adverse events leading to premature study discontinuation from Day 0 to six months after the first study vaccination.

6.3.9 Statistical Considerations & Statistical Analysis Plan
The study was performed in an observer-blinded fashion:
- Unblinded qualified study staff who were not involved with safety evaluation and other trial procedures prepared and administered the vaccine.
- Blinded Investigators and study staff who conducted safety assessments did not know which vaccine was administered.
- Subjects did not know which vaccine was administered.

Subjects were randomized in an approximately 4:1:1 ratio to one of the three study arms using an IVRS system.

Primary Analyses

Non-inferiority in terms of geometric mean titer was demonstrated if the lower limit of the two-sided 95% CI of the ratio of the GMTs (QIV divided by TIV) 28 days after final vaccination was >0.66 for each of the four virus strains after the final vaccination within each age group and overall.

Non-inferiority in terms of seroconversion rates was demonstrated if the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (QIV minus TIV) 28 days after final vaccination was >-10% for each of the four virus strains after the final vaccination within each age group and overall.

Data from the two TIVs were pooled together for each of the influenza A strains. Comparisons for the influenza B strains were done between QIV and the TIV with the corresponding influenza B strain.

Secondary Analyses

Superiority in terms of geometric mean titer was demonstrated if the lower limit of the two-sided 95% CI of the ratio of the GMTs (QIV divided by TIV) 28 days after final vaccination was >1.5 for each B strain in QIV compared with the corresponding B strain not contained in each TIV.

Superiority in terms of seroconversion rates was demonstrated if the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (QIV minus TIV) 28 days after final vaccination was >10% for each B strain in QIV compared with the corresponding B strain not contained in each TIV.

Observational Analyses

Immunogenicity

Analyses to achieve the observational immunogenicity objectives were descriptive, presenting for each strain in each of the vaccines the GMTs, fold rise in GMT, seroconversion rates, and the proportion of subjects with post-vaccination HAI titers ≥ 1:40, as described above.

Safety

Safety data were analyzed using descriptive statistics.

Study Results

6.3.10 Study Population and Disposition

This trial was conducted at 69 investigative sites in the US. The study began on 11 November 2010 and was completed on 23 January 2012. Overall, a total of 4363 subjects were randomized in Study QIV04, and 4013 (92.0%) subjects completed the study. Fifteen (0.3%) subjects were randomized but did not receive vaccine.

6.3.10.1 Populations Enrolled/Analyzed

Three analysis sets were used: the Per-Protocol Analysis Set (PP), the Full Analysis Set (FAS), and the Safety Analysis Set (SAS). Criteria for these analysis sets were the same as those described in Section 6.1.10.1.

6.3.10.1.1 Demographics

Table 27 summarizes the subject demographic and baseline characteristics.

Table 27: Study QIV04 – Demographics and Baseline Characteristics According to Randomized Vaccine Groups – All Age Groups, All Randomized.

Demographic Attribute	QIV (N=2902) n (%)	2010-2011 TIV (N=736) n (%)	Investigational TIV (N=725) n (%)	Total (N=4363) n (%)
Sex				
Male	1475 (50.8)	369 (50.1)	366 (50.5)	2210 (50.7)
Female	1427 (49.2)	367 (49.9)	359 (49.5)	2153 (49.3)
Age (Months)				
Median	43.8	44.6	43.1	43.8
Range	[6.0, 117.3]	[6.0, 107.8]	[6.0, 108.0]	[6.0, 117.3]
Race/Ethnic origin				
Black	595 (20.5)	147 (20.0)	139 (19.2)	881 (20.2)
White	1693 (58.3)	433 (58.8)	417 (57.5)	2543 (58.3)
Hispanic	415 (14.3)	97 (13.2)	108 (14.9)	620 (14.2)
Other	175 (6.0)	53 (7.2)	49 (6.8)	277 (6.3)

*Individual race/ethnicity categories other than White, Black, and Hispanic were reported at rates of <2%
Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Table 9.8 p255

The median age of study subjects was 43.8 months; the percentage of females and males was similar, and the majority of subjects were White (58.3%) or Black (20.1%). In general, the demographic characteristics were comparable among the three vaccination groups, among the two age groups (6 months to <36 months; 3 years to <9 years) and this balance was preserved in the FAS and PP analysis cohorts (not shown).

> **Reviewer comment:** *As discussed in Sections 6.1.10.1.1 and 6.2.10.1.1, antibody responses to influenza vaccination generally do not appear to differ by gender, race, or ethnicity. Nevertheless, the distribution of these characteristics in the QIV04 study population more closely approximates the general U.S. population compared to GRC43 and QIV03.*

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Not applicable

6.3.10.1.3 Subject Disposition
Overall, 4363 subjects 6 months through 8 years of age were enrolled, randomized and vaccinated in the study, comprising the Safety Analysis Set (SAS). A total of 432 (9.9%) subjects in the SAS were excluded from the Final Analysis Set (FAS) population. The most common reason for exclusion from the FAS population was the absence of a post-vaccination blood sample (9.9% of QIV subjects, 10.1% of 2010-2011 TIV subjects, and 7.7% of investigational TIV subjects). A total of 396 subjects (258 [8.9%] QIV, 74 [10.1%] 2010-2011 TIV, 64 [8.8%] investigational TIV) in the FAS were excluded from the Per-Protocol (PP) Analysis Set. The most common reason (3.4%) for exclusion from the PP analysis set was that the post-dose serum sample was outside of the visit window. A total of 350 (8.0%) subjects did not complete the vaccination phase of the study; the most common reasons were loss to follow-up and non-compliance. Analyses of patient disposition by age sub-group were not provided.

Subject disposition for the complete study population is summarized in Table 28.

Table 28: Study QIV04 – Subject Disposition According to Randomized Vaccine Groups –All Age Groups – All Randomized

Disposition	QIV n (%)	2010-11 TIV n (%)	Investigational TIV n (%)	Total n (%)
All randomized (N)	**2902 (100.0)**	**736 (100.0)**	**725 (100.0)**	**4363 (100.0)**
Safety Analysis Set	**2893 (99.7)**	**734 (99.7)**	**721 (99.4)**	**4348 (99.7)**
Received 1 dose of vaccine	720 (24.8)	161 (21.9)	181 (25.0)	1062 (24.3)
Received 2 doses of vaccine	2173 (74.9)	573 (77.9)	540 (74.5)	3286 (75.3)
Full Analysis Set	**2597 (89.5)**	**656 (89.1)**	**663 (91.4)**	**3916 (89.8)**
Did not provide a post-vaccination blood sample	286 (9.9)	74 (10.1)	56 (7.7)	416 (9.5)
Did not produce a valid serological result	8 (0.3)	5 (0.7)	3 (0.4)	16 (0.4)
Per-Protocol Analysis Set	**2339 (80.6)**	**582 (79.1)**	**599 (82.6)**	**3520 (80.7)**
Did not meet eligibility criteria	87 (3.0)	28 (3.8)	28 (3.9)	143 (3.3)
Did not receive correct number of vaccine doses	15 (0.5)	3 (0.4)	1 (0.1)	19 (0.4)
Received vaccine other than the one randomized to	1 (<0.1)	2 (0.3)	0 (0.0)	3 (0.1)
Preparation and/or administration of vaccine not done per protocol	2 (0.1)	1 (0.1)	0 (0.0)	3 (0.1)
Did not receive vaccine in proper time window	48 (1.7)	14 (1.9)	16 (2.2)	78 (1.8)
Did not provide post-dose serology in proper time window	104 (3.6)	26 (3.5)	19 (2.6)	149 (3.4)
Received a protocol-restricted therapy/medication/vaccine	1 (<0.1)	0 (0.0)	0 (0.0)	1 (<0.1)
Serology sample did not produce a valid result	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects completing the study	**2659 (91.6)**	**677 (92.0)**	**677 (93.4)**	**4013 (92.0)**
Did not complete study due to:	243 (8.4)	59 (8.0)	48 (6.6)	350 (8.0)
SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other AE	10 (0.3)	2 (0.3)	0 (0.0)	12 (0.3)
Non-compliance	72 (2.5)	24 (3.3)	15 (2.1)	111 (2.5)
Lost to follow-up	102 (3.5)	23 (3.1)	20 (2.8)	145 (3.3)
Voluntary withdrawal not due to an AE	59 (2.0)	10 (1.4)	13 (1.8)	82 (1.9)
Contact at 6-month follow-up	2553 (88.0)	659 (89.5)	654 (90.2)	3866 (88.6)
Did not complete 6-month follow-up due to SAE	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Table 9.5 p246-248

Of the 4348 subjects who received vaccine and were included in the SAS, 1062 (24.3%) received one dose, and 3286 (75.3%) received two doses. Among the two age groups, 1841 children were aged 6 - <36 months, and 2506 children were aged 3 - <9 years (one child in the SAS was >9 years of age and thus excluded from age-group analyses).

> **Reviewer comment:** *A total of 92% of subjects completed the study. Eighty percent of randomized subjects were included in the PP analysis set. While exclusion of 20% of subjects from the PP analysis is of concern, it is not unusual in a study of young infants. The reasons for exclusion from the different study populations were similar in the three study arms.*

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoints

The primary objective the study was to demonstrate non-inferiority of antibody responses to quadrivalent influenza vaccine (QIV) compared with licensed 2010-2011 trivalent influenza vaccine (TIV) (containing the recommended seasonal influenza B/Victoria strain) and investigational TIV (containing a previously recommended seasonal influenza B/Yamagata strain) as assessed by GMT ratios and seroconversion rates after the final vaccination within each age group (6 to < 36 months and 3 to < 9 years of age) and overall. For each comparison, non-inferiority was demonstrated if the lower limit of the two-sided 95% CI of the GMT ratio was >0.66, and if the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (QIV minus TIV) was > -10%. The results of the primary endpoint analyses are presented in Tables 29-32.

Table 29: Study QIV04 – Comparison of Geometric Mean Titers (GMTs) against Influenza A Strains after QIV with GMTs after TIV – All Ages - Per-Protocol Analysis Set

		QIV N=2339		Pooled TIV N=1181		Non-Inferiority Criteria Met
Antigen Strain	**n**	**GMT (95% CI)**	**n**	**GMT (95% CI)**	**Ratio of GMT (95% CI)**	
A/California/07/2009 (A/H1N1)	2337	1124 (1060, 1192)	1178	1096 (1008, 1192)	1.03 (0.93, 1.14)	Yes
A/Victoria/210/2009 (A/H3N2)	2334	822 (783, 862)	1176	828 (774, 887)	0.99 (0.91, 1.08)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Table 9.185 p2086

Table 30: Study QIV04 – Comparison of Geometric Mean Titers (GMTs) against Influenza B Strains after QIV with GMTs after TIV with Corresponding B Strain – All Ages - Per-Protocol Analysis Set

		QIV N=2339		2010-2011 TIV N=582		Investigational TIV N=599		Non-Inferiority Criteria Met
Antigen Strain	**n**	**GMT (95% CI)**	**n**	**GMT (95% CI)**	**n**	**GMT (95% CI)**	**Ratio of GMT (95% CI)**	
B/Brisbane/60/2008 (B1)	2338	86.1 (81.8, 90.6)	581	64.3 (58.3, 70.9)	--	--	1.34 (1.20, 1.50)	Yes
B/Florida/04/2006 (B2)	2338	61.5 (58.6, 64.7)	--	--	598	58.3 (52.6, 64.7)	1.06 (0.94, 1.18)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Table 9.188 p2089

Table 31: Study QIV04 – Comparison of Seroconversion Rates against Influenza A Strains after QIV with those after TIV – All Ages - Per-Protocol Analysis Set

	QIV N=2339	Pooled TIV N=1181		Non-Inferiority Criteria Met
Antigen Strain	**n/M (% [95% CI])**	**n/M (% [95% CI])**	**Difference in SCR (95% CI)**	
A/California/07/2009 (A/H1N1)	2153/2331 (92.4 [91.2, 93.4])	1076/1177 (91.4 [89.7, 93.0])	0.9 (-0.9, 3.0)	Yes
A/Victoria/210/2009 (A/H3N2)	2050/2329 (88.0 [86.6, 89.3])	989/1174 (84.2 [82.0, 86.3])	3.8 (1.4, 6.3)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Table 9.191 p2092
n is the number of subjects with a seroconversion
M is the number of subjects with a valid serology result for the particular antigen, including results reported as <LLOQ or >ULOQ
SCR = seroconversion rate

Table 32: Study QIV04 – Comparison of Seroconversion Rates against Influenza B Strains after QIV with those after TIV with Corresponding B strain – All Ages - Per-Protocol Analysis Set

	QIV N=2339	2010-2011 TIV N=582	Investigational TIV N=599		Non-Inferiority Criteria Met
Antigen Strain	**n/M (% [95% CI])**	**n/M (% [95% CI])**	**n/M (% [95% CI])**	**Difference in SCR (95% CI)**	
B/Brisbane/60/2008 (B1)	1677/2336 (71.8 [69.9, 73.6])	355/581 (61.1 [57.0, 65.1])	--	10.7 (6.4, 15.1)	Yes
B/Florida/04/2006 (B2)	1543/2335 (66.1 [64.1, 68.0])	--	383/598 (64.0 [60.1, 67.9])	2.0 (-2.2, 6.4)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Table 9.200 p2101
n is the number of subjects with a seroconversion
M is the number of subjects with a valid serology result for the particular antigen, including results reported as <LLOQ or >ULOQ
SCR = seroconversion rate

Reviewer comment: *The primary objectives of the study, which were to demonstrate immunologic non-inferiority of the antibody response to all four influenza antigens in QIV compared to the corresponding antigens in two TIV formulations based on GMT ratios and seroconversion rates, were met.*

6.3.11.2 Analyses of Secondary and Observational Endpoints

Superiority Analyses

The secondary objective of the study was to demonstrate the superiority of antibody responses to each B strain in QIV compared with antibody titers following vaccination with the TIV that does not contain the corresponding B strain, as assessed by GMT ratios and SC rates. Superiority was demonstrated if the lower limit of the two-sided 95% CI of the ratio of the GMTs (QIV divided by TIV) 28 days after final vaccination was >1.5 for each B strain in QIV compared with the corresponding B strain not contained in each TIV; and if the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (QIV minus TIV) 28 days after final vaccination was

>10% for each B strain in QIV compared with the corresponding B strain not contained in each TIV. Results of the secondary endpoint analyses are presented in Tables 33 and 34.

Table 33: Study QIV04 – Comparison of Geometric Mean Titers (GMTs) against Influenza B Strains after QIV with GMTs after TIV without Corresponding B Strain – All Ages - Per-Protocol Analysis Set

		QIV N=2339		2010-2011 TIV N=582		Investigational TIV N=599		Superiority Criteria Met
Antigen Strain	**n**	**GMT (95% CI)**	**n**	**GMT (95% CI)**	**n**	**GMT (95% CI)**	**Ratio of GMT (95% CI)**	
B/Brisbane/60/2008 (B1)	2338	86.1 (81.8, 90.6)	--	--	599	19.5 (17.4, 21.8)	4.42 (3.94, 4.97)	Yes
B/Florida/04/2006 (B2)	2338	61.5 (58.6, 64.7)	581	16.3 (14.8, 17.9)	--	--	3.79 (3.39, 4.23)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Table 9.197 p2098

Table 34: Study QIV04 – Comparison of Seroconversion Rates against Influenza B Strains after QIV with those after TIV without Corresponding B strain – All Ages - Per-Protocol Analysis Set

	QIV N=2339	2010-2011 TIV N=582	Investigational TIV N=599		Superiority Criteria Met
Antigen Strain	**n/M (% [95% CI])**	**n/M (% [95% CI])**	**n/M (% [95% CI])**	**Difference in SCR (95% CI)**	
B/Brisbane/60/2008 (B1)	1677/2336 (71.8 [69.9, 73.6])	--	120/599 (20 [16.9, 23.5])	51.8 (47.9, 55.3)	Yes
B/Florida/04/2006 (B2)	1543/2335 (66.1 [64.1, 68.0])	104/581 (17.9 [14.9, 21.3])	--	48.2 (44.3, 51.6)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Table 9.200 p2101
n is the number of subjects with a seroconversion
M is the number of subjects with a valid serology result for the particular antigen, including results reported as <LLOQ or >ULOQ
SCR = seroconversion rate

> **Reviewer comment:** *The secondary objective of the study was met, which was to demonstrate the superiority of HAI antibody responses to each B strain in QIV compared with antibody titers following vaccination with the TIV that does not contain the corresponding B strain, as assessed by GMT ratios and seroconversion rates using pre-specified success criteria.*

Descriptive Analyses

Study QIV04 also included the observational immunogenicity objective of describing the GMTs, GMT ratios, seroconversion rates, and the proportion of subjects with post-vaccination HAI titers ≥ 1:40 induced by the three vaccines among children requiring one dose, and among those requiring two doses. The results of these analyses are presented in Table 35.

Table 35: Study QIV04 – Summary of HAI Antibody Responses for Each Influenza Strain – All Age Groups, by Number of Doses Received – Per-Protocol Analysis Set

Antigen Strain		QIV N=510	2010-2011 TIV N=114	Investigational TIV N=141	QIV N=1829	2010-2011 TIV N=468	Investigational TIV N=458
		One Dose	One Dose	One Dose	Two Doses	Two Doses	Two Doses
A/California/07/2009 (A/H1N1)	Pre-Vaccination GMT	55.0	53.9	64.4	37.0	37.5	38.5
	Post-Vaccination GMT	1013	1070	1078	1157	1243	975
	GMT ratio (post/pre)	16.2	17.2	14.9	22.7	24.5	18.4
	Seroconversion rate	87.1%	85.1%	85.8%	93.8%	95.3%	90.8%
	Post-Vaccination Proportion with titers ≥ 1:40	97.6%	97.4%	98.6%	98.9%	98.9%	97.8%
A/Victoria/210/2009 (A/H3N2)	Pre-Vaccination GMT	42.3	53.2	54.8	26.2	28.9	25.0
	Post-Vaccination GMT	750	568	934	843	816	890
	GMT ratio (post/pre)	14.7	9.22	14.2	23.1	20.6	24.8
	Seroconversion rate	81.6%	72.3%	81.6%	89.8%	85.0%	87.3%
	Post-Vaccination Proportion with titers ≥ 1:40	98.8%	97.3%	97.9%	99.9%	99.6%	100.0%
B/Brisbane/60/2008(B1)	Pre-Vaccination GMT	9.16	8.85	10.9	7.97	8.45	8.20
	Post-Vaccination GMT	63.5	49.7	24.2	93.8	68.4	18.2
	GMT ratio (post/pre)	4.71	3.80	1.76	7.16	5.11	1.80
	Seroconversion rate	59.0%	50.4%	17.0%	75.4%	63.7%	21.0%
	Post-Vaccination Proportion with titers ≥ 1:40	66.9%	63.7%	39.0%	81.9%	73.9%	32.1%
B/Florida/04/2006(B2)	Pre-Vaccination GMT	8.72	8.75	9.73	7.13	7.10	7.06
	Post-Vaccination GMT	59.6	22.8	61.3	62.1	15.0	57.4
	GMT ratio (post/pre)	4.67	1.89	4.50	5.24	1.63	4.91
	Seroconversion rate	61.4%	23.9%	59.6%	67.4%	16.5%	65.4%
	Post-Vaccination Proportion with titers ≥ 1:40	68.6%	40.7%	69.5%	72.4%	26.3%	69.6%

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Tables 9.203 and 9.204, p2104-2111
[1] GMT ratio is the geometric mean of the individual post-vaccination/pre-vaccination titer ratios
[2] Seroconversion is defined as either a pre-vaccination HAI titer < 1:10 and a post-vaccination titer >= 1:40 or a pre-vaccination titer >= 1:10 and a four-fold increase in post-vaccination

> **Reviewer comment:** *Although not formally included in the evaluation of immunogenicity, fold increases in GMT and the proportion of subjects with post-vaccination HAI titers ≥ 1:40 after the last dose were generally equivalent or higher in children who received two doses (i.e., were influenza vaccine-naïve at enrollment) compared to those receiving one dose. Overall, responses against the corresponding antigens were consistent across all three vaccines.*

6.3.11.3 Subpopulation Analyses

Analyses of Non-Inferiority by Age Group

Analyses of the co-primary endpoints stratified by age group are presented in Tables 36-39.

Table 36: Study QIV04 – Comparison of Geometric Mean Titers (GMTs) against Influenza A and B Strains after QIV with GMTs after TIV – 6 - <36 months - Per-Protocol Analysis Set

		QIV		Pooled TIV (for A strains) or TIV with corresponding B strain		Non-Inferiority Criteria Met
Antigen Strain	**n**	**GMT (95% CI)**	**n**	**GMT (95% CI)**	**Ratio of GMT (95% CI)**	
A/California/07/2009 (A/H1N1)	947	747 (680, 821)	467	714 (624, 816)	1.05 (0.89, 1.23)	Yes
A/Victoria/210/2009 (A/H3N2)	944	526 (492, 562)	467	571 (517, 632)	0.92 (0.82, 1.04)	Yes
B/Brisbane/60/2008(B1)	948	72.8 (67.3, 78.7)	225	54.7 (47.2, 63.4)	1.33 (1.12, 1.59)	Yes
B/Florida/04/2006(B2)	948	36.2 (33.7, 38.8)	245	32.9 (28.7, 37.6)	1.10 (0.94, 1.28)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Table 9.186 p2087 and Table 9.189 p2090

Table 37: Study QIV04 – Comparison of Geometric Mean Titers (GMTs) against Influenza A and B Strains after QIV with GMTs after TIV – 3 - <9 years - Per-Protocol Analysis Set

		QIV		Pooled TIV (for A strains) or TIV with corresponding B strain		Non-Inferiority Criteria Met
Antigen Strain	**n**	**GMT (95% CI)**	**n**	**GMT (95% CI)**	**Ratio of GMT (95% CI)**	
A/California/07/2009 (A/H1N1)	1390	1484 (1380, 1595)	711	1453 (1312, 1609)	1.02 (0.90, 1.16)	Yes
A/Victoria/210/2009 (A/H3N2)	1390	1112 (1046, 1183)	709	1058 (971, 1154)	1.05 (0.95, 1.17)	Yes
B/Brisbane/60/2008 (B1)	1390	96.6 (90.3, 103)	356	71.2 (62.6, 81.1)	1.36 (1.17, 1.57)	Yes
B/Florida/04/2006 (B2)	1390	88.5 (83.1, 94.1)	353	86.9 (76.1, 99.2)	1.02 (0.89, 1.17)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Table 9.186 p2087 and Table 9.190 p2091

Table 38: Study QIV04 – Comparison of Seroconversion Rates against Influenza A and B Strains after QIV with those after TIV – 6 - <36 Months - Per-Protocol Analysis Set

	QIV	Pooled TIV (for A strains) or TIV with corresponding B strain		Non-Inferiority Criteria Met
Antigen Strain	**n/M (% [95% CI])**	**n/M (% [95% CI])**	**Difference in SCR (95% CI)**	
A/California/07/2009 (A/H1N1)	855/941 (90.9 [88.8, 92.6])	416/466 (89.3 [86.1, 91.9])	1.6 (-1.6, 5.1)	Yes
A/Victoria/210/2009 (A/H3N2)	897/940 (95.4 [93.9, 96.7])	431/466 (92.5 [89.7, 94.7])	2.9 (0.4, 5.9)	Yes
B/Brisbane/60/2008(B1)	681/946 (72.0 [69.0, 74.8])	146/225 (64.9 [58.3, 71.1])	7.1 (0.5, 14.1)	Yes
B/Florida/04/2006(B2)	543/945 (57.5 [54.2,60.6])	131/245 (53.5 [47.0, 59.8])	4.0 (-2.9, 11.0)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Table 9.192 p2093 and Table 9.195 p2096
n is the number of subjects with a seroconversion
M is the number of subjects with a valid serology result for the particular antigen, including results reported as <LLOQ or >ULOQ
SCR = seroconversion rate

Table 39: Study QIV04 – Comparison of Seroconversion Rates against Influenza A and B Strains after QIV with those after TIV – 3 - <9 Years - Per-Protocol Analysis Set

	QIV	Pooled TIV (for A strains) or TIV with corresponding B strain		Non-Inferiority Criteria Met
Antigen Strain	**n/M (% [95% CI])**	**n/M (% [95% CI])**	**Difference in SCR (95% CI)**	
A/California/07/2009 (A/H1N1)	1298/1390 (93.4 [91.9, 94.6])	660/711 (92.8 [90.7, 94.6])	0.6 (-1.6, 3.0)	Yes
A/Victoria/210/2009 (A/H3N2)	1153/1389 (83.0 [80.9, 84.9])	558/708 (78.8 [75.6, 81.8])	4.2 (0.7, 7.9)	Yes
B/Brisbane/60/2008 (B1)	996/1390 (71.7 [69.2, 74.0])	209/356 (58.7 [53.4, 63.9])	12.9 (7.4, 18.6)	Yes
B/Florida/04/2006 (B2)	1000/1390 (71.9 [69.5, 74.3])	252/353 (71.4 [66.4, 76.0])	0.6 (-4.5, 6.0)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Table 9.193 p2094 and Table 9.196 p2097
n is the number of subjects with a seroconversion
M is the number of subjects with a valid serology result for the particular antigen, including results reported as <LLOQ or >ULOQ
SCR = seroconversion rate

> **Reviewer comment:** *These analyses by age group confirm prior data indicating that younger children produce lower antibody titers compared to older children, but that rates of seroconversion are similar, due to higher baseline titers in the latter group. These patterns were similar in all treatment arms, and thus all non-inferiority criteria were met within the age strata.*

Analyses of Superiority by Age Group
Analyses of the secondary endpoints evaluating the superiority of the QIV influenza B responses to non-corresponding TIV stratified by age group are presented in Tables 40-43.

Table 40: Study QIV04 – Comparison of Geometric Mean Titers (GMTs) against Influenza B Strains after QIV with GMTs after TIV without Corresponding B Strain – 6 - <36 Months - Per-Protocol Analysis Set

		QIV N=949		2010-2011 TIV N=225		Investigational TIV N=245		Superiority Criteria Met
Antigen Strain	**n**	**GMT (95% CI)**	**n**	**GMT (95% CI)**	**n**	**GMT (95% CI)**	**Ratio of GMT (95% CI)**	
B/Brisbane/60/2008 (B1)	948	72.8 (67.3, 78.7)	--	--	245	12.0 (10.3, 13.9)	6.09 (5.13, 7.23)	Yes
B/Florida/04/2006 (B2)	948	36.2 (33.7, 38.8)	225	8.56 (7.68, 9.54)	--	--	4.22 (3.62, 4.93)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Table 9.198 p2099

Table 41: Study QIV04 – Comparison of Geometric Mean Titers (GMTs) against Influenza B Strains after QIV with GMTs after TIV without Corresponding B Strain – 3 - <9 Years - Per-Protocol Analysis Set

		QIV N=1390		2010-2011 TIV N=357		Investigational TIV N=354		Superiority Criteria Met
Antigen Strain	**n**	**GMT (95% CI)**	**n**	**GMT (95% CI)**	**n**	**GMT (95% CI)**	**Ratio of GMT (95% CI)**	
B/Brisbane/60/2008 (B1)	1390	96.6 (90.3, 103)	--	--	354	27.3 (23.4, 31.8)	3.54 (3.04, 4.13)	Yes
B/Florida/04/2006 (B2)	1390	88.5 (83.1, 94.1)	356	24.4 (21.6, 27.5)	--	--	3.63 (3.16, 4.16)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Table 9.199 p2100

Table 42: Study QIV04 – Comparison of Seroconversion Rates against Influenza B Strains after QIV with those after TIV without Corresponding B strain – 6 - <36 Months - Per-Protocol Analysis Set

	QIV N=949	2010-2011 TIV N=225	Investigational TIV N=245		Superiority Criteria Met
Antigen Strain	**n/M (% [95% CI])**	**n/M (% [95% CI])**	**n/M (% [95% CI])**	**Difference in SCR (95% CI)**	
B/Brisbane/60/2008 (B1)	681/946 (72.0 [69.0, 74.8])	--	36/245 (14.7 [10.5, 19.8])	57.3 (51.3, 62.1)	Yes
B/Florida/04/2006 (B2)	543/945 (57.5 [54.2, 60.6])	15/225 (6.7 [3.8, 10.8])	--	50.8 (45.7, 54.8)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Table 9.201 p2102
n is the number of subjects with a seroconversion
M is the number of subjects with a valid serology result for the particular antigen, including results reported as <LLOQ or >ULOQ
SCR = seroconversion rate

Table 43: Study QIV04 – Comparison of Seroconversion Rates against Influenza B Strains after QIV with those after TIV without Corresponding B strain – 3 - <9 Years - Per-Protocol Analysis Set

	QIV N=1390	2010-2011 TIV N=357	Investigational TIV N=354		Superiority Criteria Met
Antigen Strain	**n/M (% [95% CI])**	**n/M (% [95% CI])**	**n/M (% [95% CI])**	**Difference in SCR (95% CI)**	
B/Brisbane/60/2008 (B1)	996/1390 (71.7 [69.2, 74.0])	--	84/354 (23.7 [19.4, 28.5])	47.9 (42.6, 52.7)	Yes
B/Florida/04/2006 (B2)	1000/1390 (71.9 [69.5, 74.3])	89/356 (25.0 [20.6, 29.8])	--	46.9 (41.6, 51.7)	Yes

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Table 9.202 p2103
n is the number of subjects with a seroconversion
M is the number of subjects with a valid serology result for the particular antigen, including results reported as <LLOQ or >ULOQ
SCR = seroconversion rate

Reviewer comment: *Pre-specified criteria for demonstrating the superiority of influenza B responses in QIV over the non-corresponding TIV were met for both age groups by analysis of both GMT ratios and differences in seroconversion rates. Although GMTs against B viruses in the QIV group were nominally higher in older children compared to younger children, the GMT ratios were lower in the older children due to higher GMTs in the TIV groups. A similar effect was seen when comparing rates of seroconversion among the two age groups. This may be due to higher rates of pre-existing immunity to the non-corresponding B viruses in older children, or an increased ability among older children to mount an immune response against heterologous B viruses.*

6.3.11.4 Dropouts and/or Discontinuations
Analyses was performed on the PP analysis set as defined in the study protocol. Additional analyses on the FAS were not performed.

6.3.11.5 Exploratory and Post Hoc Analyses
Not applicable.

6.3.12 Safety Analyses
6.3.12.1 Methods
All safety analyses were conducted with the Safety Analysis Set, which included all subjects who received the study or control vaccine. Analyses were conducted according to the vaccine received rather than according to the randomization.

6.3.12.2 Overview of Adverse Events
The occurrence of immediate unsolicited AEs (within 20 minutes of injection) were reported by 9 (0.6%) of children aged 6 - <36 months and 5 (0.2%) of children aged 3 - <9 years. The incidence of solicited adverse reactions were similar in all three treatment arms, occurring in 72.3-77.6% of subjects 6-<36 months of age (57.1-62.6% experiencing injection site adverse reactions and 53.4-60.6% experiencing systemic adverse reactions) and in 76.1-77.6% of subjects 3-<9 years of age (70.2-71.7% experiencing injection site adverse reactions and 48.9-54.0% with systemic adverse reactions). Unsolicited adverse events occurred in 55.2-56.5% of subjects 6-<36 months of age (4.8-6.3% assessed as an adverse reaction) and in 41.2-44.1% of subjects 3-<9 years of age (5.8-8.3% as adverse reactions). Within the six-month follow-up period, AEs leading to discontinuation occurred in 13 subjects, SAEs occurred in 62 subjects (3 considered related to study vaccine) and death occurred in one subject (considered not related to study vaccine).

Solicited Adverse Reactions

Among subjects 6-<36 months of age, solicited injection site adverse reactions after vaccine injection were reported by 62.6% (720/1150) of subjects in the QIV group, 57.1% (165/289) of subjects in the 2010-2011 TIV group, and 57.1% (168/294) of subjects in the investigational TIV group. Among subjects 3-<9 years of age, solicited injection site adverse reactions after vaccine injection were reported by 70.2% (1118/1592) of subjects in the QIV group, 71.7% (294/410) of subjects in the 2010-2011 TIV group, and 70.6% (281/398) of subjects in the investigational TIV group.

Among subjects 6-<36 months of age, solicited systemic adverse reactions after vaccine injection were reported by 59.2% (682/1152) of subjects in the QIV group, 60.6% (175/289) of subjects in the 2010-2011 TIV group, and 53.4% (157/294) of subjects in the investigational TIV group. Among subjects 3-<9 years of age, solicited systemic adverse reactions after vaccine injection

were reported by 53.2% (847/1593) of subjects in the QIV group, 48.9% (201/411) of subjects in the 2010-2011 TIV group, and 54.0% (215/398) of subjects in the investigational TIV group.

Table 44 summarizes the solicited local and general adverse events reported within 7 days (Day 0 to 7) following vaccination, overall and those Grade 3 in intensity.

Table 44: Study QIV04 – Solicited Injection Site and Systemic Adverse Reactions after Vaccine Injection, by Maximum Intensity during the Solicited Period – All Subjects by Age Group - Safety Analysis Set

	6-<36 months	6-<36 months	6-<36 months	3-<9 years	3-<9 years	3-<9 years
	QIV (N=1223)	2010-2011 TIV (N=310)	Investigational TIV (N=308)	QIV N=1669	2010-2011 TIV N=424	Investigational TIV N=413
Subjects with at least one:	n/M (%)	n/M (%)	n/M (%)	n/M (%)	n/M (%)	n/M (%)
Pain [1]	297/521 (57.0)	68/130 (52.3)	75/149 (50.3)	1061/1592 (66.6)	265/410 (64.6)	254/398 (63.8)
Grade 3	5/521 (1.0)	1/130 (0.8)	4/149 (2.7)	33/1592 (2.1)	8/410 (2.0)	11/398 (2.8)
Tenderness [2]	340/628 (54.1)	77/159 (48.4)	72/145 (49.7)			
Grade 3	12/628 (1.9)	3/159 (1.9)	0/145 (0.0)			
Erythema	429/1150 (37.3)	95/289 (32.9)	98/294 (33.3)	543/1592 (34.1)	151/410 (36.8)	140/398 (35.2)
Grade 3	2/1150 (0.2)	0/289 (0.0)	0/294 (0.0)	29/1592 (1.8)	5/410 (1.2)	7/398 (1.8)
Swelling	248/1150 (21.6)	57/289 (19.7)	51/294 (17.3)	395/1592 (24.8)	104/410 (25.4)	103/398 (25.9)
Grade 3	2/1150 (0.2)	0/289 (0.0)	0/294 (0.0)	22/1592 (1.4)	5/410 (1.2)	7/398 (1.8)
Fever	164/1148 (14.3)	46/288 (16.0)	38/293 (13.0)	112/1591 (7.0)	29/409 (7.1)	30/396 (7.6)
Grade 3	24/1148 (2.1)	5/288 (1.7)	6/293 (2.0)	34/1591 (2.1)	5/409 (1.2)	3/396 (0.8)
Vomiting [2]	93/628 (14.8)	18/159 (11.3)	20/144 (13.9)			
Grade 3	6/628 (1.0)	1/159 (0.6)	0/144 (0.0)			
Crying Abnormal [2]	259/628 (41.2)	58/159 (36.5)	43/144 (29.9)			
Grade 3	21/628 (3.3)	3/159 (1.9)	3/144 (2.1)			
Drowsiness [2]	237/628 (37.7)	51/159 (32.1)	46/144 (31.9)			
Grade 3	8/628 (1.3)	1/159 (0.6)	1/144 (0.7)			
Headache [1]	46/517 (8.9)	12/128 (9.4)	18/148 (12.2)	368/1593 (23.1)	87/411 (21.2)	97/398 (24.4)
Grade 3	3/517 (0.6)	0/128 (0.0)	0/148 (0.0)	35/1593 (2.2)	11/411 (2.7)	8/398 (2.0)
Appetite lost [2]	203/628 (32.3)	53/159 (33.3)	36/144 (25.0)			
Grade 3	11/628 (1.8)	3/159 (1.9)	1/144 (0.7)			
Malaise [1]	197/517 (38.1)	45/128 (35.2)	48/148 (32.4)	508/1593 (31.9)	135/411 (32.8)	133/398 (33.4)

	6-<36 months	6-<36 months	6-<36 months	3-<9 years	3-<9 years	3-<9 years
	QIV (N=1223)	**2010-2011 TIV (N=310)**	**Investigational TIV (N=308)**	**QIV N=1669**	**2010-2011 TIV N=424**	**Investigational TIV N=413**
Grade 3	24/517 (4.6)	6/128 (4.7)	10/148 (6.8)	87/1593 (5.5)	23/411 (5.6)	20/398 (5.0)
Myalgia [1]	138/517 (26.7)	34/128 (26.6)	37/148 (25.0)	615/1593 (38.6)	140/411 (34.1)	153/398 (38.4)
Grade 3	10/517 (1.9)	2/128 (1.6)	4/148 (2.7)	52/1593 (3.3)	11/411 (2.7)	11/398 (2.8)
Irritability [2]	339/628 (54.0)	84/159 (52.8)	77/144 (53.5)			
Grade 3	20/628 (3.2)	5/159 (3.1)	4/144 (2.8)			

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Table 9.86 p583 and Table 9.89 p588 and Table 9.110 p628
n: number of subjects experiencing the endpoint listed in the second and third columns
M: number of subjects with available data for the relevant endpoint
[1] Assessed in children 24 months of age and older
[2] Assessed in children 6 to <= 23 months of age

Pain was the most common solicited local adverse reaction among all age groups, occurring in 50.3-66.6%, however only 0.8-2.8% were graded as severe. Among children ages 6-≤23 months, irritability was the most common solicited systemic adverse reaction, reported in 52.8-54.0%, while malaise was most common in children aged 24-<36 months (32.4-38.1%) and aged 3-<9 years (31.9-33.4%). The rates of severe (Grade 3) were highest for malaise (4.6-6.8% in all arms and both age groups). The percentage of other Grade 3 adverse reactions was <3.0% for all solicited local AE categories and <4.0% for all solicited systemic AE categories.

Fever occurred at similar rates for all vaccines, and was reported at approximately twice the rate among younger children (6-<36 months) compared to older children (3-<9 years) (13.0-16.0% vs. 7.0-7.6%, respectively). In contrast, rates of Grade 3 fever (> 103.1°F for children aged 6-≤23 months and ≥ 102.1°F for children aged 24 months-<9 years) were similarly low across all age groups and treatment arms (0.8-2.1%).

> **Reviewer comment:** *The differences in rates for each individual solicited adverse reaction were similar and did not exceed 7% for any adverse reaction. There were differences in the incidence of individual adverse reactions by age group, but these differences were similar across all treatment arms. No increase was observed in the reactogenicity of QIV compared to TIV, indicating that the higher antigen content contained in the candidate vaccine poses no additional safety risk.*

Unsolicited Adverse Events

The frequencies of the most common non-serious unsolicited adverse events are summarized in Table 45.

Table 45: Study QIV04 – Common (Reported in >10% of Subjects in Any Treatment Arm) Unsolicited Non-Serious AEs between the First Visit and the Last Visit, by Preferred Term - 6 Months to < 36 Months and 3 Years to < 9 Years - Overall - Safety Analysis Set

	6 - <36 months	6 - <36 months	6 - <36 months	3 - <9 years	3 - <9 years	3 - <9 years
	QIV (n=1223)	2010-2011 TIV (n=310)	Investigational TIV (n=308)	QIV (n=1669)	2010-2011 TIV (n=424)	Investigational TIV (n=413)
All Unsolicited Non-Serious AE	678 (55.4)	175 (56.5)	167 (54.2)	682 (40.9)	177 (41.7)	179 (43.3)
Grade 3	108 (8.8)	26 (8.4)	34 (11.0)	127 (7.6)	25 (5.9)	33 (8.0)
Cough	160 (13.1)	37 (11.9)	39 (12.7)	181 (10.8)	58 (13.7)	50 (12.1)
Pyrexia	123 (10.1)	29 (9.4)	33 (10.7)	65 (3.9)	15 (3.5)	32 (7.7)
Upper respiratory infection	120 (9.8)	33 (10.6)	29 (9.4)	64 (3.8)	10 (2.4)	18 (4.4)
Diarrhea	88 (7.2)	25 (8.1)	32 (10.4)	47 (2.8)	17 (4.0)	6 (1.5)

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Table 6.7 (p166) and Table 6.8 (p181)

> **Reviewer comment:** *The types of unsolicited AEs reported were consistent with common illnesses observed in the age groups studied. For both age groups, the occurrence of non-serious unsolicited AEs and ARs were similar across treatment groups. No imbalances were observed in terms of severity or specific diagnoses, and significant uncommon conditions were not observed at abnormally high frequencies.*

The following conditions with potentially autoimmune etiologies were reported:

- Juvenile arthritis (1 subject, investigational TIV)
- Rheumatoid arthritis (1 subject, 2010-2011 TIV)
- Henoch-Schonlein purpura (1 subject, investigational TIV)
- Erythema multiforme (1 subject, QIV)

All potentially autoimmune cases were reported in the 6-<36 month age group.

> **Reviewer comment:** *The distribution of these cases does not suggest a specific risk for the development of autoimmune disorders following vaccination with QIV.*

6.3.12.3 Deaths

One death occurred in this study. A 19-month old male died as a result of drowning 43 days after receiving a second dose of 2010-2011 TIV. The event was reported by the investigator as unrelated to the vaccine.

> **Reviewer comment:** *In this reviewer's opinion, this death was not related to study vaccine.*

6.3.12.4 Nonfatal Serious Adverse Events

Among subjects 6-<36 months of age, 30 (2.5%) subjects in the QIV group, 4 (1.3%) subjects in the 2010-2011 TIV group, and 10 (3.2%) subjects in the investigational TIV group reported SAEs after any dose. (See Table x for a summary of all SAEs). Two of these were considered by the investigator to be related to study vaccine:

- A 11 month old male who experienced a febrile seizure (axillary body temperature of 101.5°F [38.6°C]) approximately 8 hours after vaccination with a second dose of investigational TIV. The subject had symptoms of an upper respiratory tract infection (URI) for 2 days prior to Dose 2. The subject was treated with acetaminophen after the febrile seizure and recovered the same day without hospitalization. The next day, the subject was diagnosed with right ear infection. Of note, at 18 days post-vaccination, the subject experienced a second episode of febrile seizure, which was reported by the investigator as unrelated to the study vaccine.
- A 13-month-old male subject experienced croup 3 days after vaccination with QIV. The subject had no medical history of croup or any other respiratory illness. He was hospitalized for 2 days and received racemic epinephrine, dexamethasone, budesonide, and oral prednisolone. He recovered 18 days after onset of the first symptom, and received a second dose of QIV without recurrence of this event.

Among subjects 3-<9 years of age, 11 (0.7%) subjects in the QIV group, 3 (0.7%) subjects in the 2010-2011 TIV group, and 4 (1%) subjects in the investigational TIV group reported SAEs. (See Table X for a summary of all SAEs) One of these was considered by the investigator to be related to study vaccine:

- A 4-year-old male subject experienced a febrile seizure 1 day after vaccination with the first dose of 2010-2011 TIV. The subject had a medical history of febrile seizures. The

subject developed a fever to 102.6°F (39.3°C) with seizure activity that lasted for a few minutes. Treatment included oral ibuprofen. Following the treatment, the fever and seizure resolved the same day without recurrence. The subject was not hospitalized and continued in the study. The event of febrile seizure was reported by the investigator as related to the control vaccine. The subject received a second dose of the control vaccine without recurrence of this event.

Serious adverse events for both age groups are summarized in Table 46.

Table 46: Study QIV04: All SAEs Reported in at Least 2 Subjects by SOC and PT - Pediatric Population – Overall - Safety Analysis Set

	6 - <36 Months	6 - <36 Months	6 - <36 Months	3 - <9 Years	3 - <9 Years	3 - <9 Years
	QIV (N=1223)	2010-2011 TIV (N=310)	Investigational TIV (N=308)	QIV (N=1669)	2010-2011 TIV (N=424)	Investigational TIV (N=413)
Subjects with at least one:	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
SAE	**30 (2.5)**	**4 (1.3)**	**10 (3.2)**	**11 (0.7)**	**3 (0.7)**	**4 (1.0)**
Infections and infestations	**10 (0.8)**	**2 (0.6)**	**8 (2.6)**	**2 (0.1)**	**1 (0.2)**	**1 (0.2)**
Abscess	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Croup infectious	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastroenteritis	2 (0.1)	0 (0.0)	2 (0.6)	1 (0.1)	0 (0.0)	0 (0.0)
Pneumonia	1 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)
Respiratory syncytial virus bronchiolitis	3 (0.2)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Viral upper respiratory tract infection	1 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	**2 (0.2)**	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**	**0 (0.0)**	**0 (0.0)**
Femur fracture	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Nervous system disorders	**9 (0.7)**	**1 (0.3)**	**2 (0.6)**	**1 (0.1)**	**1 (0.2)**	**1 (0.2)**
Febrile convulsion	7 (0.6)	1 (0.3)	2 (0.6)	1 (0.1)	1 (0.2)	1 (0.2)
Seizure anoxic	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**5 (0.4)**	**0 (0.0)**	**1 (0.3)**	**5 (0.3)**	**1 (0.2)**	**1 (0.2)**
Asthma	3 (0.2)	0 (0.0)	0 (0.0)	5 (0.3)	0 (0.0)	0 (0.0)
Bronchial hyperreactivity	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Vascular disorders	**3 (0.2)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Kawasaki's disease	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Table 6.11, p. 205-210 and Table 6.12, p. 212-217

Reviewer comment: *No safety signals were noted in the analysis of AE's by organ system or preferred term. The percentage of subjects with SAEs was low and similar in all arms. The subject narratives for all SAEs were reviewed. Given the available information, the reviewer did not identify any additional events as potentially related to vaccination. As expected, febrile seizures, a known adverse reaction associated with influenza vaccination and other childhood vaccines, were the most common cause of a SAE (see following section).*

6.3.12.5 Adverse Events of Special Interest (AESI)

The conditions monitored in this study as AESIs included GBS, Bell's palsy, encephalitis/myelitis, optic neuritis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and febrile seizures. Among these, only febrile seizures were reported. Fourteen (14) AESIs were reported in 13 subjects, and occurred in similar proportions among the three treatment arms. Two of these events were considered related to vaccination (see previous section).

Reviewer comment: *Although febrile seizures were reported in 13 subjects, this is a small percentage of the study population (0.3%) and only 3 of the febrile seizures were reported within five days of vaccination. Of the three, two cases in control vaccine recipients were determined by the investigators to be related to vaccination. The case in a QIV recipient was judged to unrelated due to a concurrent respiratory syncytial virus infection; this reviewer concurs with the assessment of the investigator. In the opinion of this reviewer, the available evidence does not suggest a safety signal with regard to febrile seizure.*

6.3.12.6 Clinical Test Results

This study did not include any clinical laboratory evaluations.

6.3.12.7 Dropouts and/or Discontinuations

The frequencies of adverse events leading to study discontinuation are summarized in Table 47.

Table 47: Study QIV04 – Adverse Events Leading to Study Discontinuation – All Ages – Safety Analysis Set

6-<36 months	6-<36 months	6-<36 months	3-<9 years	3-<9 years	3-<9 years
QIV (N=1223) n (%)	2010-2011 TIV (N=310) n (%)	Investigational TIV (N=308) n (%)	QIV N=1669 n (%)	2010-2011 TIV N=424 n (%)	Investigational TIV N=413 n (%)
4 (0.3)	3 (1.0)	0 (0.0)	6 (0.4)	0 (0.0)	0 (0.0)

Source: Adapted from sBLA 103914/5574; Clinical Study Report QIV04, Table 6.1, p. 147, and Table 6.2, p, 150

Subjects 6-<36 months of age who discontinued due to a related AE included one subject in the QIV group with abnormal crying and irritability: one subject in the QIV group with fever; and one subject in the QIV group with hives on the face, hands, and feet. Subjects 3-<9 years of age who discontinued due to a related AE included one subject with injection site erythema, swelling, itching, and accentuated injection site adverse reaction; and one subject with malaise; both had received QIV. Listings for all AEs leading to study dropout or discontinuation were reviewed and the reviewer concurs with the determinations of relatedness.

Reviewer comment: *There was no single adverse event or class of adverse events associated with premature study discontinuation.*

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication
This clinical efficacy supplement for Fluzone Quadrivalent (QIV), an inactivated quadrivalent influenza vaccine, is intended to support an indication for active immunization in persons 6 months of age and older against influenza disease caused by influenza A subtypes and type B viruses contained in the vaccine.

7.1.1 Methods of Integration
Three studies were conducted and included in this BLA for review: Studies GRC43, QIV03, and QIV04. No additional studies were submitted in support. Across all 3 studies, 3307 subjects received QIV, 1149 subjects received licensed TIV, and 1136 subjects received an investigational TIV. However, the study populations were composed of different age groups and the influenza vaccines administered contained different influenza virus strains. Therefore, the immunogenicity data from individual studies could not be pooled. Please see Section 6 for discussions of the individual results of each study.

7.1.2 Demographics and Baseline Characteristics
The mean and median ages for the three studies reflected their respective enrollment objectives, and were well-balanced among the treatment groups within each study. The proportion of male and female subjects differed among the three studies, with the highest proportion of females in Study GRC43 (64.9-68.4%) and the lowest proportion in Study QIV04 (49.0-49.4%). Nevertheless, within each study, proportions were similar among treatment arms. The proportion of racial and ethnic minorities also differed among the trials, with the highest percentages of Black and Hispanic subjects in the pediatric study (17.3% and 14%, respectively, in QIV04, vs. 2.0% and 7.3% in QIV03, and 9.6% and 0.4% in GRC43), but again, there were no notable imbalances among vaccine groups within each study.

Reviewer comment: *Although the study populations were not all consistent with the gender and racial/ethnic distribution in the U.S. (See www.census.gov), there is no known difference in antibody response to influenza vaccine by gender, race or ethnicity.*

7.1.3 Subject Disposition
For the studies evaluating adults (GRC43 and QIV03), the proportion of randomized subjects retained in the Per Protocol analysis set ranged 97.3-100.0% across treatment arms, indicating a high degree of study compliance and retention. This proportion was comparatively lower in Study QIV04, but stable across treatment groups, ranging 79.1-82.6%. As described in Section 6.3.10.1.3, approximately half of those excluded from the PP population were excluded because of discontinuation, while the remaining had specific protocol deviations.

Protocol Deviations
Protocol deviations were uncommon in the adult trials, occurring in 5 (0.8%) of 570 subjects in Study GRC43 and 15 (2.2%) of 675 subjects in Study QIV03. In contrast, protocol deviations occurred in 842 (19.3%) of 4362 subjects in Study QIV04. The most common deviations were that the post-dose serology sample was not provided in the proper time window (4.8-8.0% per treatment arm); at least one inclusion criteria not met/at least one exclusion criteria met (5.2-5.9%); and vaccination not completed, incorrect number of doses (4.0-4.6%). However, there did not appear to be any significant imbalances among treatment arms in the study.

Reviewer comment: *The frequency of protocol deviations was significantly higher in the QIV04, as compared to the other two studies, but comparable to rates reported for pediatric vaccine trials in general. These violations occurred in all treatment arms equally, and do not appear to have affected the validity of the results.*

7.1.4 Analysis of Primary Endpoints

The ratio comparing the post-vaccination GMT in the QIV group to the post-vaccination GMT in the comparator TIV group against each strain was a primary endpoint for all three studies. For each comparison, non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio of the post-vaccination GMTs (GMTR; GMT_{QIV} divided by GMT_{TIV}) was >0.66 for each of the four virus strains (including overall and separately within each age group for QIV04). Seroconversion rate (SCR) was a co-primary endpoint in QIV04. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference in SCR (SCR_{QIV} - SCR_{TIV}) post-vaccination was >-10% for each of the four strains. Titers were measured 21 days (for Studies GRC43 and QIV03) or 28 days (for Study QIV04) after the final vaccination. Immunogenicity data from the two TIVs were pooled for each of the A strains and analyzed separately for the B strains. The GMT endpoints for all three studies are summarized in Table 48. The SCR co-primary endpoints in QIV04 are summarized in Section 7.1.6.

Table 48. All Studies – Ratio of GMTs ($GMT_{QIV}/GMT_{comparator}$) – Non-inferiority analyses – Per-Protocol Analysis Sets

	GRC43	QIV03	QIV04	QIV04	QIV04
	≥18 yr	≥65 yr	6 mo - <36 mo	3 yr - <9 yr	6 mo - <9 yr
	GMTR (95%CI)	GMTR (95%CI)	GMTR (95%CI)	GMTR (95%CI)	GMTR (95%CI)
H1N1	1.06 (0.87; 1.31)	0.85 (0.67; 1.09)	1.05 (0.89; 1.23)	1.02 (0.90; 1.16)	1.03 (0.93; 1.14)
H3N2	0.9 (0.70; 1.15)	1.55 (1.25; 1.92)	0.92 (0.82; 1.04)	1.05 (0.95; 1.17)	0.99 (0.91; 1.08)
B1	0.89 (0.70; 1.12)	1.27 (1.05; 1.55)	1.33 (1.12; 1.59)	1.36 (1.17; 1.57)	1.34 (1.20; 1.50)
B2	1.15 (0.93; 1.42)	1.11 (0.90; 1.37)	1.1 (0.94; 1.28)	1.02 (0.89; 1.17)	1.06 (0.94; 1.18)

For all: For strain A/H1N1 and A/H3N2, Ratio of GMT = $GMT_{QIV}/GMT_{Pooled\_TIV}$.
For GRC43: A/H1N1 = A/Brisbane/59/07, A/H3N2 = A/Uruguay/716/2007 X-175C, B1 = B/Brisbane/60/2008, B2 =B/Florida/04/2006
For GRC43: For strain B1, Ratio of GMT = $GMT_{QIV}/GMT_{2009\text{-}2010\ TIV}$; For strain B2, Ratio of GMT = $GMT_{QIV}/GMT_{2008\text{-}2009\ TIV}$.
For QIV03 and QIV04: A/H1N1 = A/California/07/2009, A/H3N2 = A/Victoria/210/2009, B1 = B/Brisbane/60/2008, B2 = B/Florida/04/2006.
For QIV03 and QIV04: For strain B1, Ratio of GMT = $GMT_{QIV}/GMT_{2010\text{-}2011\ TIV}$; for strain B2, Ratio of GMT = $GMT_{QIV}/GMT_{Investigational\ TIV}$

Reviewer comment: *Non-inferiority criteria were met for all four strains for all three studies, as well as for the two age subgroups in QIV04.*

7.1.5 Analysis of Secondary Endpoints

Secondary endpoints were only included in Study QIV04, and are discussed in relation to similarly defined observational objectives in the following section.

7.1.6 Observational Endpoints

Non-inferiority Comparisons

Studies QIV03 and QIV04 included the analysis of non-inferiority using the difference in seroconversion rates between the QIV group and the comparator TIV group. This was an observational objective in QIV03 and a co-primary objective in QIV04. For each comparison, non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio of the difference in seroconversion rates (SCR_{QIV} minus the SCR_{TIV}) was >-10% for each of the four virus strains (including overall and separately within each age group for QIV04). Immunogenicity data from the two TIVs were pooled for each of the A strains and analyzed separately for the B strains. Results for these studies are summarized in Table 49.

Table 49. Studies QIV03 and QIV04 – Difference in Seroconversion Rates (QIV-TIV) – All Four Influenza Strains

	QIV03	QIV04	QIV04	QIV04
	≥65 yr	6 mo - <36 mo	3 yr - <9 yr	6 mo - <9 yr
	Difference in SCR (%) (95%CI)	Difference in SCR (%) (95%CI)	Difference in SCR (%) (95%CI)	Difference in SCR (%) (95%CI)
H1N1	-3.86 (-11.5; 3.56)	1.59 (-1.61; 5.15)	0.554 (-1.65; 3.00)	0.945 (-0.920; 2.95)
H3N2	9.77 (1.96; 17.2)	2.94 (0.369; 5.93)	4.2 (0.676; 7.88)	3.78 (1.37; 6.31)
B1	9.91 (1.96; 17.7)	7.1 (0.468; 14.1)	12.9 (7.39; 18.6)	10.7 (6.39; 15.1)
B2	1.96 (-6.73; 10.6)	3.99 (-2.93; 11.0)	0.554 (-4.52; 5.99)	2.03 (-2.19; 6.39)

For strain A/H1N1 and A/H3N2, Difference in SC rates = SC $rate_{QIV}$ minus SC $rate_{Pooled\ TIV}$.
For strain B1, Difference in SC rates = SC $rate_{QIV}$ minus SC $rate_{2010\text{-}2011\ TIV}$; for strain B2, Difference in SC rates = SC $rate_{QIV}$ minus SC $rate_{Investigational\ TIV}$.

> **Reviewer comment:** *Non-inferiority criteria were met for all comparisons except for the A/H1N1 strain in Study QIV03 (≥65 yr). As discussed in Section 6.2.11.2, the failure to meet this single observational endpoint may be related to a higher prevalence of seropositivity against this strain at baseline. In addition, this observational endpoint was marginally missed, and the evaluation of the primary GMT endpoint associated with this strain was successful in this study.*

Superiority Comparisons

Additional observational endpoints included assessments for superiority in GMTs and seroconversion rates against influenza B strains in QIV against those in the TIV that did not contain the corresponding B strain (i.e., a comparison of QIV influenza B strain responses to cross-reacting [heterologous] TIV B strain responses). For the GMT comparison, superiority was demonstrated if the lower limit of the two-sided 95% CI of the ratio of the GMTs (GMT_{QIV}/GMT_{TIV}) 21 days (for Study QIV03) or 28 days (for Study QIV04) post-vaccination was > 1.5 for each B strain in QIV compared with the corresponding B strain not contained in each TIV. Results are summarized in Table 50.

Table 50. Studies QIV03 and QIV04 – Ratio of GMTs ($GMT_{qiv}/GMT_{comparator}$) – Influenza B Strains

	QIV03	QIV04	QIV04	QIV04
	≥65 yr	6 mo - <36 mo	3 yr - <9 yr	6 mo - <9 yr
	GMTR (95%CI)	GMTR (95%CI)	GMTR (95%CI)	GMTR (95%CI)
B1	1.75 (1.43; 2.14)	6.09 (5.13; 7.23)	3.54 (3.04; 4.13)	4.42 (3.94; 4.97)
B2	2.14 (1.74; 2.65)	4.22 (3.62; 4.93)	3.63 (3.16; 4.16)	3.79 (3.39; 4.23)

B1 = B/Brisbane/60/2008, B2 = B/Florida/04/2006.
For strain B1, Ratio of GMT = $GMT_{QIV}/GMT_{Investigational\ TIV}$; for strain B2, Ratio of GMT = $GMT_{QIV}/GMT_{2010\text{-}2011\ TIV}$

For seroconversion rate comparison, superiority was demonstrated if the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (SCR_{QIV} minus SCR_{TIV}) 21 days (for Study QIV03) or 28 days (for Study QIV04) post-vaccination was >10% for each B strain in QIV compared with the corresponding B strain not contained in each TIV. Results are summarized in Table 51.

Table 51. Studies QIV03 and QIV04 – Difference in Seroconversion Rates (QIV-TIV) – Influenza B Strains

	QIV03	QIV04	QIV04	QIV04
	≥65 yr	6 mo - <36 mo	3 yr - <9 yr	6 mo - <9 yr
	Difference in SCR (%) 95%CI	Difference in SCR (%) 95%CI	Difference in SCR (%) 95%CI	Difference in SCR (%) 95%CI
B1	20.04 (12.9; 27.0)	57.3 (51.5; 62.1)	47.9 (42.6; 52.7)	51.8 (47.9; 55.3)
B2	24.05 (16.6; 31.2)	50.8 (45.7; 54.8)	46.9 (41.6; 51.7)	48.2 (44.3; 51.6)

B1 = B/Brisbane/60/2008, B2 = B/Florida/04/2006.
For strain B1, Difference in SC rates = SC $rate_{QIV}$ minus SC $rate_{Investigational\ TIV}$; for strain B2, Difference in SC rates = SC $rate_{QIV}$ minus SC $rate_{2010\text{-}2011\ TIV}$.

> **Reviewer comment:** *The observational objectives of demonstrating the superiority of B strain responses for QIV to cross-reactive B responses in the TIVs were achieved for all groups except for the GMT ratio for the B1 (B/Brisbane/60/2008) strain in the QIV03 population,but the primary objective of demonstrating the non-inferiority of GMT responses between QIV and the TIV containing the corresponding B strain was achieved.*

7.1.7 Subpopulations

Analyses by Age Group

The results of three studies were submitted to support the safety and effectiveness of Fluzone Quadrivalent. In these studies, adults 18 years of age and older were enrolled in GRC43, adults 65 years and older were studied in QIV03, and children from 6 months to < 9 years were enrolled in QIV04. In GRC43, subjects were stratified into two age subgroups, 18-60 years and

≥60 years. Due to differences in the age cohorts studied, influenza antigens included in the study vaccines, and in statistical design, it is not possible to compare results in older subjects in GRC43 and QIV03.

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In QIV04, subjects were stratified into two age subgroups, 6-<36 months and 3-<9 years of age. In general, post-vaccination GMT's were higher in the older age group compared to the younger. Nevertheless, GMTs in the younger age groups were still sufficient to result in similar rates of seroconversion in both age groups.

> **Reviewer comment:** *Differences among the subpopulations were consistent across the vaccine arms in all studies, indicating that these variabilities are related more to age than to the specific vaccines. The data from Studies QIV04 and GCR43 can be extrapolated to support the licensure of Fluzone Quadrivalent in children 9 through17 years of age, because the immune response to influenza vaccination in children and adolescents 9 through 17 years of age is similar to that observed in adults and because influenza vaccine safety data in subjects 9 through 17 years of age is similar to safety observed in children 6 months to <9 years and in adults.*

7.1.8 Persistence of Efficacy

The persistence of efficacy or immunogenicity of QIV was not evaluated in any of the studies included in this submission.

7.1.9 Product-Product Interactions

The effects of concomitantly administered medications, including vaccines, were not evaluated in any of the studies included in this submission.

7.1.10 Additional Efficacy Issues/Analyses

There were no additional concerns or analyses.

7.1.11 Efficacy Conclusions

Sanofi Pasteur submitted the results of three studies, GRC43, QIV03, and QIV04 to support the effectiveness of Fluzone Quadrivalent in persons 6 months of age and older. The primary objective of the three trials was to demonstrate that the immune response to influenza antigens in QIV were noninferior to those against a seasonal TIV with an influenza B strain of either the Victoria or Yamagata lineage. The quadrivalent influenza vaccine met all pre-specified primary endpoints, demonstrating non-inferiority to the comparator trivalent influenza vaccines based on the comparison of geometric mean titers in QIV03 and QIV04, and the comparison of seroconversion rates in QIV04. In addition, the studies met the majority of observational endpoints assessing non-inferiority based on rates of seroconversion and evaluation of superiority to cross-reactive influenza B lineage responses. These results indicate that the inclusion of a second influenza B strain of alternate lineage should provide an immunologic benefit in most seasons.

In addition, these studies included subjects from 6 months to < 9 years and 18 years and older. The results support the effectiveness of Fluzone Quadrivalent in all age groups.

In the opinion of this reviewer, the results from the pivotal Studies GRC43, QIV03, and QIV04 submitted in this supplement support the effectiveness of QIV.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The safety population from the three studies submitted in this supplement provides a database of 5592 subjects, 3307 of whom received QIV. The safety of QIV in comparison to TIV was assessed in the three studies by the following methods:

- Immediate AEs (unsolicited AEs reported in the x minutes post-vaccination)
- Solicited Local and Systemic Adverse Reactions
    - Solicited injection site adverse reactions (see Table x)
    - Solicited systemic adverse reactions (see Table x)
- All unsolicited Adverse Events
- Serious Adverse Events
- Adverse Events of Special Interest (AESI
    - Only collected for QIV03 and QIV04
    - AESIs included new onset of Guillain-Barré syndrome, Bell's palsy, encephalitis/myelitis, optic neuritis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and (for QIV04 only) febrile seizures

Vaccine doses and schedules were consistent with U.S. recommendations for inactivated influenza vaccines and are consistent with the intended use for QIV. Concomitant vaccine administration was not evaluated for safety or immunogenicity. The size of the safety populations and monitoring periods for AE assessments for each study are summarized in Table 52.

Table 52. Safety Populations and AE Monitoring Periods for Studies GCR43, QIV03, and QIV04 – Safety Analysis Sets.

Study Name	N (SAS)	Age Group	Treatment (n)	Immediate AE Period	Solicited AE Period	Unsolicited AE Period	SAE Period	AESI Period
GCR43	570	≥18 yr	1 dose of: QIV (190), 2009-2010 TIV (190), or 2008-2009 TIV (190)	20 min	3 days	21 days	21 days	n/a
QIV03	675	≥65 yr	1 dose of QIV (225), 2010-2011 TIV (225), or Investigational TIV (225)	20 min	7 days	21 days	21 days	21 days
QIV04	4347	6 mo - <9 yr	1 or 2 doses [1] of: QIV (2892)[2], 2010-2011 TIV (734), or Investigational TIV (721)	20 min	7 days after each dose	28 days or 56 days	6 months	6 months

Source: Adapted from sBLA 103914/5574; m 2.7.4 Table 1.1 and 1.2 (p10-13)
[1] Number of doses according to ACIP guidance
[2] One subject was 117 months old and received QIV as randomized. She was included in the trial population tables of the QIV CSR but was not included in any age-specific analyses.

Of note, GRC43 was conducted as an open-label study, which may have resulted in some reporting bias. In contrast, QIV03 and QIV04 were randomized and observer-blinded. In the

opinion of this reviewer, the size of the database and the methods for evaluation are adequate to assess the safety of QIV.

8.2 Safety Database

8.2.1 Clinical Trials Used to Evaluate Safety

Studies GRC43, QIV03, and QIV04 were included in the integrated analysis of safety.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The demographic characteristics of the safety populations are summarized in Table 53. In studies GRC43 and QIV03, there were more females than males enrolled; QIV04 was evenly divided by gender. Subjects in GRC43 and QIV03 were predominantly White and non-Hispanic, while the pediatric population of QIV04, the largest trial, was more racially and ethnically diverse. Given these factors, QIV04 was therefore the most similar to its corresponding target United States population.

Table 53: All Studies – Demographics and Baseline Characteristics by Randomized Vaccine Groups – Safety Analysis Set

	GRC43	GRC43	GRC43	QIV03	QIV03	QIV03	QIV04	QIV04	QIV04
	QIV (N=190)	2009-2010 TIV (N=190)	2008-2009 TIV (N=190)	QIV (N=225)	2010-2011 TIV (N=225)	Investigational TIV (N=225)	QIV (N=2890)	2010-2011 TIV (N=735)	Investigational TIV (N=722)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gender n (%)									
Male	60 (31.6)	61 (32.1)	66 (34.7)	96 (42.7)	99 (44.0)	104 (46.2)	1470 (50.9)	369 (50.2)	365 (50.6)
Female	130 (68.4)	129 (67.9)	124 (65.3)	129 (57.3)	126 (56.0)	121 (53.8)	1420 (49.1)	366 (49.8)	357 (49.4)
Age (years)*									
Median	61.6	61.0	60.8	71.1	71.9	71.	43.9	44.7	43.
Min; Max	18.1; 89.8	20.1; 88.2	18.8; 87.3	65.1; 92.2	65.0; 94.6	65.1; 92.3	6.01; 108	5.98; 108	6.01; 108
Race/Ethnicity n									
American Indian or Alaska Native	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	9 (0.3)	1 (0.1)	3 (0.4)
Asian	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.9)	2 (0.9)	13 (0.4)	5 (0.7)	7 (1.0)
Black	13 (6.8)	23 (12.1)	19 (10.0)	9 (4.0)	4 (1.8)	2 (0.9)	594 (20.6)	146 (19.9)	138 (19.1)
White	173 (91.1)	165 (86.8)	166 (87.4)	197 (87.6)	202 (89.8)	205 (91.1)	1688 (58.4)	433 (58.9)	417 (57.8)
Hispanic	0 (0.0)	1 (0.5)	1 (0.5)	19 (8.4)	17 (7.6)	14 (6.2)	412 (14.3)	97 (13.2)	106 (14.7)
Native Hawaiian or Pacific	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.3)
Other	3 (1.6)	1 (0.5)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	172 (6.0)	53 (7.2)	49 (6.8)

Source: Adapted from sBLA 103914/5574; m 2.7.4 Table 1.13 p36
N: total number of subjects per group from the safety analysis set.
n: number of subjects experiencing the endpoint listed in the first column.
Percentages are based on Ns in each column header.
* For study QIV04 the age is displayed in Months.

The extent of exposure for each vaccine is summarized in Table 54. In Study QIV04, the dose administered was 0.25 mL for subjects 6-<36 months of age, and 0.5 mL for subjects 3-<9 years of age. Most (75.3%) subjects in QIV04 were unprimed, and thus required two doses.

Table 54. All Studies – Exposure for Each Vaccine by Study – Safety Analysis Set

Study, Dose, and Regimen	Licensed TIV	Investigational TIV	QIV
GRC43, 0.5 mL, 1 dose	380	--	190
QIV03, 0.5 mL, 1 dose	225	225	225
QIV04, 0.5 mL, 1 dose	105	126	480
QIV04, 0.5 mL, 2 doses	319	287	1189
QIV04, 0.25 mL, 1 dose	56	55	239
QIV04, 0.25 mL, 2 doses	254	253	984

Source: Adapted from sBLA 103914/5574; Clinical Study Reports GRC43 Table 9.6 (p185), QIV03 Table 9.3 (p145), and QIV04 Table 9.6 (p249) and Table 9.7 (p 252)

8.2.3 Categorization of Adverse Events

Adverse events were reported in the Clinical Study Reports as Preferred Terms using the MedDRA dictionary. The verbatim terms used by the investigator for the adverse event were provided in the datasets.

8.3 Caveats Introduced by Pooling of Data Across Clinical Trials

Age-related differences in immunogenicity, safety, and tolerability related to inactivated influenza vaccines have been well documented in the scientific literature. Therefore, the applicant did not combine safety datasets from the three studies for the integrated analysis. In addition, as described in Section 8.1, safety assessment methods differed by age group, including which specific local and systemic adverse reactions were solicited and the duration of follow-up for unsolicited AEs, SAEs, and AESIs). Finally, GRC48 was an open-label study and the other two were conducted in an observer-blinded fashion. However, the subjects in GRC43 and QIV03 who were in the ≥65 years age group were considered sufficiently similar by the applicant, thus both separate and pooled analyses were presented. Safety data from the two age groups in QIV04 (6-<36 months and 3-<9 years) were evaluated both separately and combined.

8.4 Safety Results

8.4.1 Deaths

No deaths were reported in Study GRC43 or Study QIV03. One death occurred in Study QIV04. As described in Section 6.3.12.3, a 19 month old male died as a result of drowning 43 days after receiving a second dose of 2010-2011 TIV. The reviewer concurs with the applicant in assessing this event as unrelated to the vaccine.

8.4.2 Nonfatal Serious Adverse Events

Adult Subjects

Table 55 summarizes all SAEs for adult subjects in Study GRC43 and QIV03. In GRC43, two subjects experienced one or more SAEs; none were judged to be related to vaccination. In QIV03, three subjects experienced one or more SAEs, none of which were judged to be related to vaccination. Among subjects aged ≥65 years overall, SAEs occurred in 0.7% of TIV recipients and in none of the QIV recipients. Further details are provided in Section 6.1.12.4 and 6.2.12.4.

Table 55: Studies GRC43 and QIV03: All Non-fatal SAEs by SOC and PT - Adult Population - Safety Analysis Set (SAEs Reported in > One Subject)

	GRC43	GRC43	GRC43	QIV03	QIV03	QIV03	Combined ≥65	Combined ≥65
	QIV (N=190)	2009-2010 TIV (N=190)	2008-2009 TIV (N=190)	QIV (N=225)	2010-2011 TIV (N=225	Investigational TIV (N=225)	QIV (N=292)	TIV (N=568)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
SAE	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	2 (0.9)	1 (0.4)	0 (0.0)	4 (0.7)
Eye disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
Retinal detachment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Infections and infestations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
Cellulitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
Neoplasms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Malignant melanoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)

Pediatric Subjects
Non-fatal SAEs for pediatric subjects in Study QIV04 are reviewed in Section 6.3.12.4. As described, a total of 41 (1.4%) subjects in the QIV group, 7 (1.0%) subjects in the 2010-2011 TIV group, and 14 (1.9%) subjects in the investigational TIV group reported SAEs after any dose. Three subjects experienced SAEs (1 QIV, 1 2010-2011 TIV, 1 investigational TIV) that were considered related to study vaccine (two cases of febrile seizure and one of croup). The most common SOC in the 6-<36 months age sub-group was Infections and Infestations, while the Respiratory, Thoracic, and Mediastinal Disorders SOC was most common in the 3-<9 years age sub-group. No increased incidence of a single adverse event or a system organ class was observed. Serious adverse events were consistent with the population studied. AESIs were included as SAEs, and are discussed separately in section 8.4.8.

8.4.3 Study Dropouts/Discontinuations
No adverse events leading to study dropouts or premature study discontinuation were reported in GRC43. In QIV03, one subject who received the 2010-2011 TIV experienced two AEs (pruritis and diarrhea) that led to premature study discontinuation; both AEs were considered by the investigator to be related to study vaccine. In QIV04, 10 subjects who received QIV and 3 subjects who received 2010-2011 TIV experienced adverse events leading to study dropout or discontinuation. AEs leading to dropout/discontinuation were determined to be related to vaccination for 5 of the subjects who had received QIV. These subjects included one with abnormal crying and irritability; one with fever; one with hives on the face, hands, and feet; one with injection site erythema, swelling, itching, and accentuated reaction; and one with malaise.

8.4.4 Common Adverse Events
In Study GRC43, unsolicited non-serious AEs were reported in 17.4%, 23.7% and 24.2% of QIV, 2009-2010 TIV, and 2008-2009 TIV recipients, respectively. The most common Preferred Terms were headache, cough, and oropharyngeal pain.

In Study QIV03, unsolicited non-serious AEs were reported in 12.4%, 9.8%, and 9.8% of QIV, 2010-2011 TIV, and Investigational TIV recipients, respectively. The most common Preferred Terms were oropharyngeal pain and rhinorrhea (for QIV), injection site induration and oropharyngeal pain (for 2010-2011 TIV), and headache (for Investigational TIV).

In the analysis combining subjects aged ≥65 years in both studies, unsolicited non-serious AEs occurred in 13.7% of QIV recipients and 12.3% of recipients who received either TIV.

In Study QIV04, among subjects 6-<36 months of age, unsolicited non-serious AEs were reported in 55.4%, 56.5%, and 54.2% of QIV, 2010-2011 TIV, and Investigational TIV recipients, respectively. The most common Preferred Terms were cough and pyrexia (for QIV and Investigational TIV), and cough and URI (for 2010-2011 TIV).

Among subjects 3-<9 years of age, unsolicited non-serious AEs were reported in 40.9%, 41.7%, and 43.3% of QIV, 2010-2011 TIV, and Investigational TIV recipients, respectively. The most common Preferred Terms were cough and vomiting (QIV and 2010-2011 TIV), and cough and pyrexia (Investigational TIV).

As discussed in the individual study reviews, no increased incidence of a unsolicited single adverse event or of adverse events in a single system organ class was observed. Unsolicited adverse events reported were consistent with the populations studied..

8.4.5 Clinical Test Results
There were no clinical safety laboratory tests performed in any of the studies submitted to this supplemental BLA.

8.4.6 Systemic Adverse Events

The occurrence of individual solicited systemic adverse reactions in the three studies is described in Section 6 of this review and summarized in Table 56. The most commonly reported solicited systemic adverse events in adult subjects were headache, malaise and myalgia. Interestingly, although GRC43 was an open-label study and QIV03 was an observer-blind study, the percentage of subjects with individual solicited systemic adverse events was generally high in subjects in GRC43. However, the incidence of all solicited systemic adverse reactions was similar between the treatment arms in the studies and was generally consistent with, if not lower than, the rate of solicited adverse reactions in the licensed trivalent Fluzone package insert.

Table 56. All Studies – Occurrence of All Individual Solicited Systemic Adverse Reactions – Safety Analysis Sets

	GRC43	GRC43	GRC43	QIV03	QIV03	QIV03		QIV04	QIV04	QIV04	QIV04	QIV04
							3-<9 years	3-<9 years	3-<9 years	6-<36 months[1]	6-<36 months	6-<36 months
	QIV	2009-2010 TIV	2008-2009 TIV	QIV	2010-2011 TIV	Investigl TIV	QIV	2010-2011 TIV	Investigl TIV	QIV	2010-2011 TIV	Investigl TIV
	N=190	N=190	N=413	N=225	N=225	N=225	N=1669	N=424	N=413	N=1223	N=310	N=308
Fever	0	0.5	0.5	1.3	0	0.9	7	7.1	7.6	14.3	16	13
Grade 3	0	0	0	0.4	0	0.4	2.1	1.2	0.8	2.1	1.7	2
Headache	15.8	18.4	18	13.4	11.6	11.6	23.1	21.2	24.4	8.9	9.4	12.2
Grade 3	0.5	0.5	0	0.4	0	0.4	2.2	2.7	2	0.6	0	0
Malaise	10.5	14.7	12.1	6.3	11.6	9.6	31.9	32.8	33.4	38.1	35.2	32.4
Grade 3	1.1	1.1	0.5	0.4	0	0.9	5.5	5.6	5	4.6	4.7	6.8
Myalgia	23.7	25.3	16.8	18.3	18.3	14.2	38.6	34.1	38.4	26.7	26.6	25
Grade 3	0	0	0	0.4	0	0.4	3.3	2.7	2.8	1.9	1.6	2.7
Shivering	2.6	5.3	3.2	--	--	--	--	--	--	--	--	--
Grade 3	0	0	0	--	--	--	--	--	--	--	--	--
Vomiting	--	--	--	--	--	--	--	--	--	14.8	11.3	13.9
Grade 3	--	--	--	--	--	--	--	--	--	1	0.6	0
Crying Abnormal	--	--	--	--	--	--	--	--	--	41.2	36.5	29.9
Grade 3	--	--	--	--	--	--	--	--	--	3.3	1.9	2.1
Drowsiness	--	--	--	--	--	--	--	--	--	37.7	32.1	31.9
Grade 3	--	--	--	--	--	--	--	--	--	1.3	0.6	0.7
Appetite lost	--	--	--	--	--	--	--	--	--	32.3	33.3	25
Grade 3	--	--	--	--	--	--	--	--	--	1.8	1.9	0.7
Irritability	--	--	--	--	--	--	--	--	--	54	52.8	53.5
Grade 3	--	--	--	--	--	--	--	--	--	3.2	3.1	2.8

[1] Systemic adverse reactions solicited in children 6-<24 months were fever, vomiting, abnormal crying, drowsiness, loss of appetite, and irritability; and in children 24 months-<9 years were fever, headache, malaise, and myalgia.

The most commonly reported solicited adverse reactions in subjects 6 to < 36 months of age who received QIV were irritability, abnormal crying, malaise, and drowsiness. The most commonly reported in subjects 3 to < 9 years of age who received QIV were myalgia, malaise, and headache. The incidence of individual systemic adverse reactions was similar in the QIV and TIV arms. Of note, fever was reported in 13%-16% of subjects in the 6 to <36 month age group and in 7%-7.6% of subjects in the 3 to < 9 year age group. Grade 3 fever was reported in 2.1% or less of all pediatric subjects. There was no increase in all fever or Grade 3 fever in the QIV arms.

8.4.7 Local Reactogenicity

The occurrence of individual solicited local adverse reactions in the three studies is described in Section 6 of this review and summarized in Table 57. In the two adult studies, pain was the most common solicited injection site adverse reaction, reported in 47% of subjects receiving QIV in GRC43 and in 33% of subjects receiving QIV in QIV03. In GRC43, the incidence of pain was similar in the QIV and TIV arms; pain at the injection site was reported in 52% and 43% of subjects in the two TIV arms. In QIV03, pain was reported slightly more often in the QIV arm compared to the TIV arms (29% and 23%). Grade 3 pain was uncommon in both studies and was reported in in <1% of subjects..

In Study QIV04, tenderness were solicited in subjects 6-23 months and pain in subjects 2 to < 9 years of age. Pain was reported in 57% of subjects 24 to <36 months of age and in 67% of subjects 3 to <9 years of age. Grade 3 pain was reported in less than 3% of pediatric subjects. Tenderness was reported in 54% of subjects 6 to 23 months of age. Erythema was reported in approximate one-third of subjects in both age groups. The incidence of subjects with swelling at the injection site ranged from 17 to 26%. Grade 3 erythema and swelling were uncommon (<2%). Overall, the incidence of individual local solicited adverse reactions was similar between treatment arms and in each age cohort. There was no marked increase in adverse injection site reactions associated with the increased antigen content of QIV.

Table 57. All Studies – Occurrence of All Individual Solicited Local Adverse Reactions – Safety Analysis Sets

	GRC43			QIV03			QIV04 3-<9 years	QIV04 3-<9 years	QIV04 3-<9 years	QIV04 6-<36 months	QIV04 6-<36 months	QIV04 6-<36 months
	2010-2011 TIV	2008-2009 TIV	QIV	QIV	2010-2011 TIV	Investigl TIV	QIV	2010-2011 TIV	Investigl TIV	QIV	2010-2011 TIV	Investigl TIV
	(N=190)	(N=190)	(N=190)	(N=225)	(N=225)	(N=225)	N=1669	N=424	N=413	N=1223	N=310	N=308
Pain	52.1	43.2	47.4	32.6	28.6	23.1	66.6	64.6	63.8	57	52.3	50.3
Grade 3	0.5	0	0.5	0.9	0	0	2.1	2	2.8	1	0.8	2.7
Erythema	1.6	1.6	1.1	2.7	1.3	1.3	34.1	36.8	35.2	37.3	32.9	33.3
Grade 3	0	0	0	0	0	0	1.8	1.2	1.8	0.2	0	0
Swelling	3.2	1.1	0.5	1.8	1.3	0	24.8	25.4	25.9	21.6	19.7	17.3
Grade 3	0	0	0	0	0	0	1.4	1.2	1.8	0.2	0	0
Induration	1.6	0.5	0.5	--	--	--	--	--	--	--	--	--
Grade 3	0	0	0	--	--	--	--	--	--	--	--	--
Ecchymosis	0.5	0.5	0.5	--	--	--	--	--	--	--	--	--
Grade 3	0	0	0	--	--	--	--	--	--	--	--	--
Tenderness	--	--	--	--	--	--	--	--	--	54.1	48.4	49.7
Grade 3	--	--	--	--	--	--	--	--	--	1.9	1.9	0

Injection site adverse reactions solicited in children 6-<24 months were tenderness, erythema, and swelling; and in children 24 months-<9 years were pain, erythema, and swelling.

8.4.8 Adverse Events of Special Interest
Adverse events of special interest (AESIs) were not monitored in GRC43. No AESIs were observed in QIV03, and febrile seizures were the only AESIs observed in QIV04. See Section 6.3.12.5 for a discussion of these AEs.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events
Compared to TIV formulations, QIV contains a higher content of hemagglutinin antigen in each dose (60 µg in QIV compared to 45 µg in TIV). The submitted data do not indicate any increase in the reactogenicity of QIV compared to TIV.

8.5.2 Time Dependency for Adverse Events
In studies of QIV, adverse events in adults were assessed up to 21 days, whereas children were monitored for SAEs through 6 months post-vaccination. Most adverse events occurred within 3 days of administration.

8.5.3 Product-Demographic Interactions
Not applicable

8.5.4 Product-Disease Interactions
Not applicable

8.5.5 Product-Product Interactions
Not applicable

8.5.6 Human Carcinogenicity
Not applicable

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound
Not applicable

8.5.8 Immunogenicity (Safety)
Not applicable

8.5.9 Person-to-Person Transmission, Shedding
Not applicable

8.6 Safety Conclusions
QIV appears to have an acceptable safety profile in healthy pediatric, adult, and geriatric populations, comparable to the currently licensed Fluzone trivalent inactivated influenza vaccine. Overall, the safety evaluation of QIV generates no particular safety concerns. In the opinion of this reviewer, these studies support the safety of QIV for use in individuals 6 months and older according to recommended dosing and schedules.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data
No human reproductive or toxicity data were provided in this supplement.

9.1.2 Use During Lactation
Fluzone Quadrivalent has not been evaluated in nursing mothers. It is not known if the vaccine is excreted in human milk.

9.1.3 Pediatric Use and PREA Considerations
For children 6 months to <9 years of age, PREA requirements were fulfilled by the submission of safety and immunogenicity data from Study QIV04.

The safety and immunogenicity of Fluzone Quadrivalent in pediatric patients are supported by the results of studies QIV04 (conducted in subjects 6 months to < 9 years of age). In addition, in Study GRC43 Fluzone Quadrivalent was demonstrated to be safe and effective in subjects 18 years of age and older. The data from the age groups studied in QIV04 and GRC43 can be extrapolated to support the licensure of Fluzone Quadrivalent in children 9-17 years of age, because the immune response to influenza vaccination in children and adolescents 9 to 17 years of age is similar to that observed in adults and because influenza vaccine safety data in subjects 9 to 17 years of age is typically similar to safety observed in children 6 months to <9 years and in adults.

The PREA requirement for studies in children ages 0 to <6 months were waived, because available data in infants <6 months of age indicate that serum antibody responses to inactivated influenza vaccines in this age group are not as robust as in older children due to 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 this vaccine is not likely to be used in a substantial number of infants < 6 months of age.

9.1.4 Immunocompromised Patients
Fluzone Quadrivalent has not been studied in immunocompromised patients.

9.1.5 Geriatric Use
Elderly subjects were enrolled in Studies GRC43 and QIV03. In GRC43, enrollment was stratified to ensure an equal number of subjects in two age groups: 18-60 years and 61 years and older. Please see Section 6 for a discussion of each of these studies.

10. CONCLUSIONS
The clinical data submitted in this supplement support the safety and effectiveness of Fluzone Quadrivalent in persons 6 months of age and older. The clinical recommendation is for traditional approval, based on the demonstration of non-inferior immunogenicity for the three influenza strains included in the currently licensed Fluzone vaccine and superiority for the B strains not included in the trivalent vaccine, as well as a similar safety profile compared to the licensed Fluzone trivalent vaccine.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

A comparison of risks and benefits of licensure of Fluzone Quadrivalent for use in persons 6 months of age and older is presented in Table 58 and discussed in Section 11.2

Table 58: Risk-Benefit Considerations for licensure of Fluzone Quadrivalent.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Influenza infects 5-20% of the population each year with a wide range of severity, including up to 200,000 hospitalizations, 3,000-44,000 deaths in the US annually - Morbidity/mortality highest among the very young, the elderly, and those with underlying medical conditions - Roughly 10% of hospitalizations result in death, mostly in elderly - Since the late 1980s, two antigenically distinct B virus lineages have circulated, sometimes concurrently; - Influenza can cause pandemics	- Influenza is a major cause of morbidity/mortality in the US - A substantial proportion of infections result in serious or life-threatening disease, particularly among high-risk groups - Illnesses caused by influenza B viruses represent a considerable proportion of overall influenza disease burden

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Unmet Medical Need	- The neuraminidase inhibitor class of antivirals are available for post-exposure chemoprophylaxis; however, they must be given twice daily; are only available in oral and inhaled formulations; and provides protection only during the time when administered - Resistance to one class of antivirals is now widespread, and strains resistant to oseltamivir have circulated widely in the past - Trivalent influenza vaccines containing one A/H1N1 strain, one A/H3N2 strain, and one B strain have been available since 1980 -The effectiveness of inactivated influenza vaccines has been estimated to be approximately 59%, and there is an extensive record of safety - Vaccine effectiveness is lower among the very young, the elderly, and among those with certain chronic underlying medical conditions; and is lower in situations of antigenic mismatch - Trivalent influenza vaccines contain one influenza B strain; this strain has been optimally matched to the lineage of the circulating viruses only half the time in the past 13 years; modeling studies suggest a moderate reduction in cases if both B lineages are included in a quadrivalent vaccine, depending on B virus incidence, vaccine effectiveness, and vaccine supply for the specific season - Fluzone is the only influenza vaccine approved down to 6 months and the only inactivated vaccine approved for individuals under 3 years	- Antivirals are effective for influenza prevention, but are operationally difficult to use, and resistance is a frequent concern - Currently licensed influenza vaccines are effective against antigenically matched strains, and are well tolerated - Inclusion of both B lineages as part of a quadrivalent vaccine is projected to provide additional benefit in most seasons - There are only two currently licensed quadrivalent influenza vaccines, and neither are approved for children 6 through 23 months of age

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Clinical Benefit	- Three trials evaluating safety and immunogenicity were submitted in this supplement, one in adults aged ≥18 years, one in adults aged ≥65 years, and one in children aged 6 months to less than 9 years. The trials compared the quadrivalent vaccine to two trivalent formulations, each containing one of the two B lineages included in the quadrivalent vaccine. - The trials were well-controlled, and designed with CBER advice - Effectiveness was demonstrated using hemagglutination inhibiting (HI) titers; the vaccine was compared to an active control using the GMT ratio and the difference in seroconversion rates as co-primary endpoints, adapted from criteria developed for the approval of seasonal trivalent influenza vaccines - The Fluzone Quadrivalent met all immunologic criteria for non-inferiority against all four strains compared to trivalent vaccines in children and younger adults; and met 10 of 12 immunologic non-inferiority and superiority criteria in elderly individuals; two secondary endpoints were marginally missed in this age group - Based on CBER agreement, demonstration of efficacy based on a clinical endpoint is not necessary, as long as safety and immunogenicity of the quadrivalent vaccine are shown to be non-inferior to trivalent vaccines and manufacturing methods are sufficiently similar	- Non-inferiority criteria for immunogenicity used in this evaluation are well recognized and appropriate for this evaluation - Results of the studies in this supplement demonstrated the non-inferiority of Fluzone Quadrivalent to trivalent vaccine in all age groups - These immunogenicity results indicate that Fluzone Quadrivalent is very likely to confer protection against influenza similar to that provided by trivalent Fluzone for the strains common to both vaccines, and additional protection for the alternate B lineage over that provided by the trivalent vaccine

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk	- Fluzone vaccines have an extensive record of safety - As recommended by CBER, a total of 3307 individuals exposed to the vaccine comprise the safety database for Fluzone Quadrivalent - The most substantial risks of vaccination with Fluzone Quadrivalent identified in clinical trials are associated with local adverse reactions at the injection site, observed in all age groups. - Systemic adverse reactions, including fever, malaise, and irritability, were common in influenza-naïve young children, but none of these reactions resulted in a serious adverse event (such as hospitalization or febrile seizure) among those receiving Fluzone Quadrivalent. - Most solicited adverse reactions were mild in severity, and all resolved within a small number of days without sequelae - New onset neurologic disorders and other specifically monitored serious adverse events did not occur at an increased frequency among Fluzone Quadrivalent recipients; no other safety signals were identified in the trials submitted in the supplement	- The safety database is of adequate size to support licensure - The risks of vaccination with Fluzone Quadrivalent appear to be minor, and similar to that associated with trivalent Fluzone - Safety was not evaluated in pregnant women and nursing mothers

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	- The most common adverse reactions following vaccination with Fluzone Quadrivalent, including local injection site reactions and systemic reactogenicity, are mild and self-limited - High-quality data regarding the risks of influenza vaccination in pregnant women are limited, but the evidence available in the literature to date does not indicate that there is a safety signal.	- The risks observed in the trials submitted in support of Fluzone Quadrivalent licensure will be summarized in the package insert - As a post-marketing commitment, the applicant proposed a pregnancy registry in which pregnant women exposed to Fluzone Quadrivalent would be encouraged to contact the company to enroll in the registry and provide information. CBER asked the applicant to conduct a prospective, cohort study in exposed and unexposed pregnant women assessing safety through active surveillance The applicant responded that their original proposal for a passive registry was in accordance with the guidelines, and this was accepted by CBER.

11.2 Risk-Benefit Summary and Assessment

Based on the demonstration of non-inferiority in antibody responses (HAI) in comparison to responses to licensed trivalent influenza vaccine, and superiority of HAI responses to influenza B strains in comparison to those to alternate lineages, the data submitted to this BLA supplement establish a substantial likelihood of clinical benefit in the general population for persons 6 months of age and older receiving Fluzone Quadrivalent for the prevention of influenza and reduction in the risk of influenza-related complications. No safety signals for serious adverse events were identified, and the safety profile of QIV is similar to what is already described for trivalent Fluzone. The observed adverse reactions following vaccination of Fluzone Quadrivalent were minimal and self-limited, and will be described adequately in the package insert. In the opinion of this reviewer, Fluzone Quadrivalent presents a favorable overall risk-benefit profile.

11.3 Discussion of Regulatory Options

This supplement contains immunogenicity data using hemagglutination inhibiting antibody titer to support vaccine effectiveness, but no clinical data demonstrating prevention of influenza disease. While prevention of influenza disease is the outcome of interest, comparative clinical endpoint efficacy studies were not required for licensure of this supplement. CBER determined that comparative immunogenicity data in relation to Fluzone would be sufficient to demonstrate effectiveness, because of the similarity of the manufacturing process for Fluzone Quadrivalent vaccine compared to the licensed Fluzone trivalent vaccine, and the extensive pre- and post-licensure experience with Fluzone. (see section 2).

11.4 Recommendations on Regulatory Actions

In the opinion of this reviewer, the safety and immunogenicity data provided in this supplement support the traditional approval of Fluzone Quadrivalent for individuals 6 months of age and older.

11.5 Labeling Review and Recommendations

With this supplement, the applicant submitted a request for review of the proposed proprietary name Fluzone -(b)(4)-, with Fluzone -(b)(4)- as an alternate. A consultation from the OCBQ/Division of Case Management/Advertising and Promotional Labeling Branch (APLB) was requested. APLB reviewers found the proposed proprietary names to be unacceptable, as Fluzone -(b)(4)- was considered fanciful, and Fluzone -(b)(4)- posed a potential risk for confusion with trivalent formulations of Fluzone. CBER proposed the proprietary name of Fluzone Quadrivalent, as this is the descriptor the agency is recommending to all quadrivalent influenza vaccine manufacturers. The applicant accepted the proposed name.

Revisions to the package insert and carton and container labels were negotiated with the applicant. The main issues included the descriptions of the clinical studies and the presentation of data on solicited adverse reactions in the package insert.

No need was identified for the development of a Medication Guide or patient package insert under a REMS.

11.6 Recommendations on Postmarketing Actions

No safety signals were identified in pre-licensure data and thus no postmarketing requirement was judged to be necessary. Public health authorities currently recommend influenza vaccination among pregnant women, due to the higher risk of severe disease and complications during pregnancy, to protect both the mother as well as their newborns by the transfer of maternal antibody. However, data regarding the safety of influenza vaccines during pregnancy are limited. To improve the quality of these data, CBER recently formulated a policy encouraging the establishment of postmarketing studies that are more consistent with the August 2002 *FDA Guidance to Industry: Establishing Pregnancy Exposure Registries*. Therefore, CBER requested

the applicant to establish a prospective cohort study with active recruitment of exposed and unexposed women. The study would include patient interviews and medical record review, and would have pre-specified statistical power to rule out or detect differences in outcomes based on sample size. The applicant responded that their proposed pregnancy registry, in which pregnant women exposed to Fluzone Quadrivalent would be encouraged to contact the company to enroll in the registry and provide information, was in accordance with the guidelines. The applicant views the goal of their registry to be hypothesis generating rather than hypothesis testing. CBER found this response to be acceptable, and agrees to the proposed design of the registry.