

Application Type	Supplemental Biologics License Application
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CBER Received Date	October 17, 2012
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Division / Office	DVRPA/OVRR
Priority Review	No
Reviewer Name(s)	Roshan Ramanathan, MD, MPH Melisse Baylor, MD
Review Completion Date / Stamped Date	August 15, 2013
Supervisory Concurrence	Jeffrey Roberts, MD
Applicant	ID Biomedical Corporation of Quebec, (a subsidiary of GlaxoSmithKline Biologicals)
Established Name	Influenza Virus Vaccine
(Proposed) Trade Name	FluLaval Quadrivalent
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Quadrivalent, split virion, inactivated influenza virus vaccine provided in multi-dose vials including thimerosal as preservative
Dosage Form(s) and Route(s) of Administration	Suspension for injection available in 5 mL multi-dose vials containing ten 0.5 mL doses to be administered by intramuscular injection
Dosing Regimen	-In children 3 through 8 years of age not previously vaccinated with influenza vaccine, two doses (0.5 mL each) administered at least 4 weeks apart -In children 3 through 8 years of age vaccinated with influenza vaccine in a previous season, one or two doses (0.5 mL each), depending on vaccination history as per the annual Advisory Committee on Immunization Practices recommendation on prevention and control of influenza with vaccines. If two doses, administer each 0.5- mL dose 4 weeks apart. -In children 9 years of age and older, one 0.5 mL dose
Indication(s) and Intended Population(s)	FluLaval Quadrivalent is a vaccine indicated for active immunization for the prevention of disease caused by the influenza A subtype viruses and type B viruses contained in the vaccine. FluLaval Quadrivalent is approved for use in persons 3 years of age and older.

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## GLOSSARY

ACIP	Advisory Committee on Immunization Practices
AE	adverse event
ATP	According To Protocol
BLA	biologics license application
CDC	Centers for Disease Control
CHMP	Committee for Medical Products for Human Use (EMA)
CI	Confidence interval
CFR	Code of Federal Regulation
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
eCTD	electronic Common Technical Document
EMA	European Medicines Agency
ELISA	Enzyme-Linked Immunosorbent Assay
ES	Executive Summary
FDAAA	Food and Drug Administration Amendments Act of 2007
GMR	geometric mean ratio
GMT	geometric mean titer
GRMP	good review management principles
GSK	GlaxoSmithKline Biologicals
HA	hemagglutinin
HI	hemagglutinin inhibition
ICF	informed consent form
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ILI	Influenza Like Illness
IND	Investigational New Drug application
ISE	integrated summary of efficacy
ISS	integrated summary of safety
ITT	intent-to-treat
LL	lower limit
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
NCT	National Clinical Trials
N/E	non-evaluable
PI	Package Insert
pIMD	potential immune-mediated disease
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
QIV	Quadrivalent Influenza Vaccine
Q-QIV	QIV formulation of FluLaval
RMS/BLA	regulatory management system for the biologics license application

RT-PCR reverse-transcriptase polymerase chain reaction  
SAE serious adverse event  
SCR seroconversion rate  
(b)(4) ----(b)(4)-----  
TIV trivalent influenza vaccine  
TVC Total Vaccinated Cohort  
UL upper limit  
VE Vaccine Efficacy

## 1. EXECUTIVE SUMMARY

With this supplement, ID Biomedical Corporation of Quebec (a subsidiary of GlaxoSmithKline Biologicals) seeks licensure of FluLaval Quadrivalent Influenza Vaccine (FluLaval QIV) for active immunization against influenza disease caused by the influenza A subtype viruses and type B viruses contained in the vaccine. FluLaval QIV is intended for use in persons 3 years of age and older.

Until recently, the predominant strategy for prevention of influenza disease relied on the trivalent inactivated influenza vaccine (TIV) containing two influenza A strains (H1N1 and H3N2) and one influenza B strain (either B/Yamagata or B/Victoria). Each year, the Vaccines and Related Biological Products Advisory Committee of the FDA makes recommendations regarding which influenza A strains and which influenza B virus strain (Yamagata or Victoria) to include in the TIV vaccine for the upcoming influenza flu season. However, in recent years, co-circulation of two B lineages has contributed to a substantial burden of influenza disease. Influenza B accounts for 16% of influenza-associated deaths in adults 65 years of age and older and 46% of all influenza related deaths in children below the age of 5 years (1, 2). As inactivated influenza vaccines are most effective against strains matched to those contained in the vaccine, a TIV-based vaccination strategy does not provide adequate coverage against the influenza B strain not contained in the vaccine. In order to address the gaps in coverage afforded by TIV vaccines containing only one B strain, influenza vaccine manufacturers have developed QIV vaccines containing two influenza A strains and two B strains. To date, QIV formulations of Fluzone®, Fluarix®, and FluMist® have been licensed for use in the U.S.

FluLaval QIV is a quadrivalent, inactivated seasonal influenza vaccine manufactured using the same process as the currently licensed FluLaval®, containing antigens from two influenza A subtype viruses (representing the H1N1 and H3N2 subtypes) and two type B viruses (representing the Victoria and Yamagata lineages). The efficacy of FluLaval QIV was demonstrated in a randomized, observer-blind, controlled clinical endpoint study in 5200 children 3 through 8 years of age. The primary endpoint was prevention of reverse-transcriptase polymerase chain reaction (RT-PCR)-confirmed influenza A and/or B disease presenting as influenza like illness (ILI) caused by community acquired influenza strains. In this study, the influenza attack rate in FluLaval QIV recipients (2.4%) was lower than the influenza attack rate in control recipients (5.3%). The study estimated an absolute vaccine efficacy of 55.4% (LL of 95% CI was 39%), which satisfied the pre-specified criterion for demonstration of effectiveness (LL 95% CI > 30%). The effectiveness of FluLaval QIV in children 8 through 17 years and in adults 18 years of age and older was demonstrated in two double-blind, randomized, controlled safety and immunogenicity studies. In both studies, control groups received one of two formulations of TIV, each containing one of the two lineage B viruses. Antibody responses to FluLaval QIV were non-inferior to TIV antibody responses for influenza A subtypes and

corresponding B lineages, and superior to the opposite B lineage (e.g. B\Yamagata in Q-QIV vs. B\Victoria in TIV-VB).

No major safety concerns associated with FluLaval QIV were identified. The rates of systemic solicited adverse events were similar in the TIV and FluLaval QIV groups. Although FluLaval QIV causes increased injection site pain when compared to TIVs, these reactions were generally mild, demonstrating that the addition of a second type B virus antigen to the QIV formulation does not lead to substantially increased reactogenicity. The rates of solicited AEs across all study groups were also comparable to rates observed in studies of other inactivated influenza vaccines in the relevant age group. No imbalances in the frequency or severity of any single unsolicited AEs or group of AEs were observed among the treatment arms within each study, and no increase in serious or uncommon conditions were observed in any group.

No discipline reviewer on the BLA committee identified any known serious risk or signal of a serious risk for FluLaval QIV that would warrant additional pharmacovigilance measures (postmarketing safety study or Risk Evaluation and Mitigation Strategy). The Applicant has agreed to establish a pregnancy registry to prospectively enroll women exposed to FluLaval QIV during pregnancy and collect data on their outcomes and newborn health status, as a postmarketing commitment. The protocol will be submitted by October 31, 2013 and the registry will be established by November 30, 2013.

The safety, immunogenicity and efficacy data submitted to this supplement fulfilled the requirements of the Pediatric Research Equity Act (PREA) for children 3 through 17 years of age. A waiver from the PREA requirement for children from birth to 6 months of age was granted because vaccination in this age group provides 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 under 6 months of age. Studies in children 6 through 36 months of age were deferred for this application because the product is ready for approval in persons 3 years of age and older, and pediatric studies in ages 6 through 36 months of age have not been conducted. The Applicant committed to conduct a randomized, observer-blind, immunogenicity and safety study comparing FluLaval QIV to a US-licensed QIV influenza vaccine in children 6 through 35 months of age, as required under 505B (a) of the Federal Food, Drug and Cosmetic Act. The protocol for this study is expected on June 30, 2014, and the proposed date for submission of the study results is March 31, 2016.

In the opinion of the clinical reviewers, the data provided in this supplement support the traditional approval of FluLaval QIV for active immunization of persons 3 years of age and older against influenza disease caused by the influenza subtypes A and lineage B viruses contained in the vaccine. The minimal risks associated with FluLaval Quadrivalent vaccine, considered with the demonstrated efficacy in preventing influenza disease in children, and the added protection



expected in children and adults from broader coverage of influenza B strains, results in a favorable overall risk-benefit determination

## 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 and 3,000 to 49,000 deaths are attributed to influenza each year (2, 3). 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 U.S.), 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.

Over the past 20 years, two antigenically distinct type B virus lineages, known as B/Victoria and B/Yamagata, 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. At a 2009 meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting, panelists suggested expanding influenza vaccines to contain four virus strains: A/H1N1, A/H3N2, and one strain from each of the 2 type B lineages. On February 2012, VRBPAC voted to include vaccine strain B/Brisbane/60/2008 from the Victoria lineage in QIV vaccines produced for the upcoming influenza season (2013-2014).

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

Two classes of antivirals against influenza, the adamantane derivatives 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.

Inactivated whole-virus influenza vaccines have been commercially available since the 1940s. Currently, eight inactivated split-virus, subunit or recombinant influenza vaccines are licensed in the U.S., including the TIV formulation of FluLaval®. Of these, four are approved for individuals less than 18 years of age (Fluzone®, Fluarix®, Fluvirin®, Afluria®). FluMist®, a live, attenuated intranasal vaccine is approved for use in children 2 years through 49 years of age. QIV formulations of Fluzone, Fluarix, and FluMist are licensed for use in the United States.

## **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 neuraminidase 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 is recommended annually.

Vaccine efficacy estimates of influenza vaccines vary depending on several factors, such as the characteristics of vaccinees and the match between influenza viruses circulating in the community and the viruses contained in the vaccine. A recent meta-analysis of 31 randomized studies conducted between 1967 and 2011 calculated a pooled efficacy of 59% in healthy adults against laboratory-confirmed influenza illness (6).

The most frequent AEs 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) (7). 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.

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

FluLaval QIV is manufactured using the same process as the currently licensed FluLaval TIV vaccine, with a type B strain of a second lineage added to the seasonal TIV formulation. Hence, the previous human experience related to FluLaval TIV is relevant to FluLaval QIV.

FluLaval QIV has not been licensed by any other regulatory authorities. FluLaval TIV has been marketed in the U.S. since 2006. FluLaval (and its international trade names Fluviral® and GripLaval®) is licensed in sixteen countries. Since product launch, more than --(b)(4)-- doses have been distributed worldwide. No safety signals have been identified through postmarketing surveillance or post-market studies for FluLaval since U.S. FDA licensure.

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

FDA licensed the TIV formulation of FluLaval on October 5, 2006 for the prevention of influenza subtypes A and type B viruses contained in the vaccine under the accelerated approval regulations (21 CFR 601.41) for use in adults 18 years of age and older. Under these regulations, FDA grants accelerated approval based on a surrogate endpoint considered reasonably likely to predict that vaccine recipients will derive clinical benefit from the product. The regulations further require that, following accelerated approval, the Applicant study the biological product to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. FluLaval met the criteria for demonstration of immunogenicity described in the FDA Guidance for Industry, “Clinical Data Needed to Support the Licensure of Trivalent Inactivated Vaccines.” As per the accelerated approval regulations, the approval letter contained a postmarketing commitment (PMC) to conduct a non-inferiority study in adults  $\geq 50$  years of age and a postmarketing requirement (PMR) to conduct a clinical endpoint study in adults 18 through 49 years of age. On August 20, 2010, GSK submitted a supplemental BLA with data from a clinical efficacy study to support the traditional approval of FluLaval in adults 18 years of age and older (IND # 14466). This study demonstrated that vaccine efficacy against vaccine-matched, culture-confirmed influenza strains was 46.3% (LL of the one-sided 97.5% CI was 9.8%). The pre-defined criterion for demonstration of vaccine efficacy was not met. FDA determined that clinical benefit had not been sufficiently verified and described by this study, and did not grant traditional approval of FluLaval. The statistical analysis plan assumed an influenza attack rate of 2% in placebo recipients; the observed influenza attack rate was 1.2%. For this reason, the study may have been underpowered to meet its objectives. A clarification letter was issued on June 1, 2011, containing PREA-related PMRs for: 1) a non-inferiority study comparing FluLaval to Fluzone in children 3 through 17 years of age; and 2) a clinical endpoint efficacy study of FluLaval Quadrivalent in children 3 through 8 years of age (see Items d and e below). In STN 125163/176 GSK submitted results of two clinical studies to address the PMC

and PMR of the October 5, 2006, approval letter. Because the results of the clinical endpoint study did not demonstrate effectiveness, the accelerated approval PMR was not fulfilled. To address this issue, the approval letter of June 9, 2011 contained a new PMR for a clinical endpoint study of FluLaval Quadrivalent in children 3 through 8 years of age. On June 29, 2012, a type B pre-supplemental BLA meeting was held to discuss the proposed clinical contents of the planned supplemental BLA and pediatric development plan for FluLaval QIV. In this meeting, CBER and GSK discussed the secondary objective of the pivotal clinical endpoint study, which was the prevention of “moderate to severe influenza” disease. CBER communicated that decisions regarding the results for this objective would be a review issue.

In the current supplement, STN 125163/253, the Applicant seeks traditional approval of a QIV formulation of FluLaval based on the results of a clinical efficacy study in children 3 through 8 years of age, and three additional studies demonstrating supportive immunogenicity in children (3 through 17 years of age), adults (18 years through 64 years of age), and geriatric adults (65 years of age and older).

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----- (b)(4) -----  
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### **3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES**

#### **3.1 Submission Quality and Completeness**

The submission was 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 clinical studies submitted in this supplement except one were generally conducted in accordance with Good Clinical Practice, the Declaration of Helsinki, International Conference on Harmonization (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. A protocol compliance violation occurred at study site # 84424 in study FLU Q-QIV-006. Diary cards were not provided to subjects at this site; therefore GSK excluded data from this site. The 45 subjects enrolled at this site represented 0.9% of all subjects in this study.

CBER Bioresearch Monitoring (BIMO) conducted inspections at three sites for study FLU Q-QIV-006 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 integrity of data submitted to the supplement. Please see the review by Anthony D. Hawkins, Consumer Safety Officer, Bioresearch Monitoring Branch, Division of Inspections and Surveillance, Office of Compliance and Biologics Quality, for details

### **3.3 Financial Disclosures**

According to the Applicant, ID Biomedical Corporation of Quebec does not compensate investigators according to study outcome. Therefore, there are no disclosures for compensation that might have affected the outcome of the studies in this supplement [as required in 21 CFR 54.2 (a), (b), and (f)]. There were also no significant payments (\$25,000 or more) to any clinical investigator, and no investigator had a \$50,000 or more equity interest in the study vaccine [as required in 21 CFR 54.4 (a) (3) (iii-iv), 54.2(b-c)].

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

### **4.1 Chemistry, Manufacturing, and Controls**

FluLaval QIV uses the same manufacturing process as the licensed FluLaval TIV, except that an additional B strain is included at the formulation step. For details regarding the chemistry, manufacturing, and controls data submitted in support of this supplement, please refer to the review by Dr. Ewan Plant, OVR/Division of Viral Products.

### **4.2 Assay Validation**

The hemagglutinin inhibition (HI) assay quantified functional anti-HA antibody titers in four clinical trials (FLU Q-QIV-003, FLU Q-QIV-006, FLU Q-QIV-007, FLU Q-QIV-(T+)-009). The HI assay performed in GSK's (b)(4) Laboratory was determined by FDA to be sufficiently validated during the review of BLA 125127/SN 513 for Fluarix QIV.

Documentation was provided to validate the HI assay in GSK's (b)(4) Laboratory. A standard operating procedure, validation report and a bridging study comparing serology results from clinical studies to support the transfer of the protocol from (b)(4) were provided. FDA assay reviewers determined that the HI assay performed at (b)(4) and used to evaluate sera from studies of FluLaval QIV was considered sufficiently validated.

The methods used for antigenic typing by culture were validated. The quantitative-RT-PCR assays used to determine the primary endpoint of clinical efficacy were also shown to be well controlled and suitable for intended use.

Please refer to the review by Dr. Tielin Qin, OBE/Division of Biostatistics/Vaccine Evaluation Branch for additional details regarding the statistical analysis of the validation reports provided by the Applicant.

#### **4.3 Nonclinical Pharmacology/Toxicology**

The Applicant performed a reproductive and developmental toxicity study in female rats at a dose 80-fold the human dose (on a mg/kg basis). The study did not demonstrate impaired female fertility or harm to the fetus due to FluLaval QIV. Animals were administered FluLaval QIV by intramuscular injection twice prior to gestation, during the period of organogenesis (gestation days 3, 8, 11, and 15), and during lactation (day 7), 0.2 mL/dose/rat (80-fold higher than the projected human dose on a body weight basis). No adverse effects on mating, female fertility, pregnancy, parturition, lactation parameters, and embryo-fetal or pre-weaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis.

These results support a Pregnancy Category B label designation for FluLaval QIV.

For additional details, please see review by Dr. Steven Kunder, Pharmacologist, Division of Related Products Applications, Office of Vaccine Research and Review.

#### **4.4 Mechanism of Action**

Vaccination against influenza results in an immune response that can be quantified by elevation in HI titers. Although specific levels of HI titers have not been proven to correlate with protection from influenza illness, some studies and meta-analyses associate HI titers  $\geq 1:40$  with 50% reduction in the risk of contracting influenza, based on controlled, influenza challenge studies in adults.

#### **4.5 Statistical**

The statistical reviewer verified that the primary study endpoint analyses cited by the Applicant were supported by the submitted data. Please see review by Dr. Sang Ahnn, OBE/Division of Biostatistics/Vaccine Evaluation Branch for details.

#### **4.6 Pharmacovigilance**

No potential safety concerns were identified by reviewers of this supplement, and routine pharmacovigilance was considered an acceptable strategy. The Applicant agreed to establish a pregnancy registry as a postmarketing commitment. Review of the pharmacovigilance plan for FluLaval QIV was conducted by Dr. Craig Zinderman, Associate Director for Product Safety, Division of Epidemiology, Office of Biostatistics and Epidemiology.

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

### **5.1 Review Strategy**

This review focused on the results from four Phase 3 clinical trials, FLU Q-QIV-006, FLU Q-QIV-007 and FLU Q-QIV-003 and FLU Q-QIV-(T+)-009. Results from the pivotal clinical endpoint study, FLU Q-QIV-006, provided the basis for traditional approval of FluLaval QIV. Study FLU Q-QIV-003 included an additional, open-label cohort of 301 children 6 through 35 months of age. The results of this cohort was submitted to this BLA supplement, but those data are not emphasized because the proposed indication is for individuals 3 years of age and older. The results of study FLU Q-QIV-(T+)-009, an open-label, single arm study of the FluLaval QIV formulation containing thimerosal, were viewed as contributory to the immunogenicity and safety of FluLaval QIV.

Drs. Roshan Ramanathan and Melisse Baylor jointly reviewed this supplement. Dr. Ramanathan was the lead reviewer and was responsible for writing the Executive Summary and the Risk-Benefit Assessment. Dr. Ramanathan reviewed studies FLU Q-QIV-007 and FLU Q-QIV 006. Dr. Melisse Baylor reviewed studies FLU Q-QIV-003 and FLU Q-QIV 009.

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

The Clinical Study Reports (CSRs), pertinent case report tabulations and forms (module 5), labeling (module 1), financial information (module 1), clinical overview (module 2), pediatric waiver request and clinical summaries (module 2) were reviewed. In addition, amendments to the supplement (1, 2, 3, 4, 8, 11-19 and 21) were also reviewed.

### **5.3 Table of Studies/Clinical Trials**

Table 1 lists the completed studies submitted to the supplement and included in the clinical review.

**Table 1. Clinical Studies Included in Supplemental BLA for FluLaval QIV**

Study Name	Phase	Country (year)	Population	Objective(s)	Study Design and Type of Control	Test Products, Dosage Regimen, Route of Administration	Number of Subjects (TVC)	Duration of Study
FLU Q-QIV-003	3	Canada, Mexico, Spain, Taiwan, USA (2010-2011)	Healthy children, 6 months – 17 years	Immunogenicity of Q-QIV in children 3-17 years of age; noninferiority to TIV vaccine and superiority of 4 <sup>th</sup> B strain; Immunogenicity of Q-QIV in children 6-35 months of age; safety	Randomized, double-blind, controlled, with 3 parallel treatment groups in children 3-17 years of age, and a separate open-label Q-QIV arm in children 6-35 months of age	Q-QIV; TIV-VB; TIV-YB  Subjects dosed based on vaccination status <sup>a</sup>  IM administration	3-17 years of age; Q-QIV=932; TIV-VB=929; TIV-YB=932;  6-35 months of age: Q-QIV=301	Primary phase: 28 days after last vaccination  Safety follow up: 6 months
FLU Q-QIV -006	3	Bangladesh, Dominican Republic, Honduras, Lebanon, Panama, Philippines, Thailand, Turkey (2010-2011)	Children in stable health 3-8 years	Efficacy of Q-QIV in the prevention of influenza A and/or B disease compared to a non-influenza vaccine;  Immunogenicity and safety	Randomized, observer-blind, controlled, with 2 parallel treatment groups	Q-QIV; Havrix  Subjects dosed based on vaccination status <sup>a</sup>  IM administration	Q-QIV=2584  Havrix = 2584	Primary phase: 28 days after last vaccination  Safety follow up: at least 6 months
FLU Q-QIV -007	3	Canada, Mexico, USA (2010-2011)	Adults in stable health ≥18 years	Immunogenicity (lot-to-lot consistency of Q-QIV, superiority to 4 <sup>th</sup> strain, non-inferiority to TIV vaccine)	Randomized, double-blind, controlled, with 5 parallel treatment groups	Q-QIV-1 (lot 1) Q-QIV-2 (lot 2) Q-QIV-3 (lot 3) TIV-VB TIV-YB	Q-QIV groups=1272 (425/lot) TIV-VB=213 TIV-YB=218	Primary phase: 21 days  Safety follow up: 6 months
FLU Q-QIV-(T+)-009	3	Canada (2011-2012)	Adults in stable health ≥18 years	Immunogenicity and safety	Open, single group with age-stratification	Q-QIV (T+): 1 dose administered on day 0; IM administration	Q-QIV=112	21 days

TVC= total vaccinated cohort; Q-QIV= FluLaval Quadrivalent; IM=intramuscular; TIV-VB= trivalent inactivated influenza vaccine containing B/Yamagata; TIV-YB= trivalent inactivated influenza vaccine containing B/Victoria. T+=thimerosal added

<sup>a</sup>Subjects vaccinated with influenza vaccine in a previous season received 1 dose on day 0; Subjects not previously vaccinated with influenza vaccine received 2 doses on days 0 and 28.

Source: Adapted from sBLA 125163/SN 253; Module 2.7.3; Table 1, page 13



## 5.4 Literature Reviewed

1. World Health Organization. (2009) Influenza (Seasonal). WHO Fact Sheet No. 211. accessed at: [www.who.int/mediacentre/factsheets/fs211/en](http://www.who.int/mediacentre/factsheets/fs211/en)
2. 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.
3. 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.
4. 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.
5. Reed C, Meltzer MI, Finelli L, Fiore A. Public health impact of including two lineages of influenza B in a QIV seasonal influenza vaccine. *Vaccine*. 2012 Mar 2;30(11):1993-8.
6. 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.
7. IOM (Institute of Medicine), 2012. Adverse effects of vaccines: evidence and causality. Washington, DC: The National Academies Press.
8. 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.
9. 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]
10. 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.

11. Saurwein-Teissl M, Steger MM, Glück R, Cryz S, Grubeck-Loebenstien B. Influenza vaccination in a healthy geriatric population: preferential induction of antibodies specific for the H3N2 influenza strain despite equal T cell responsiveness to all vaccine strains. *Vaccine*. 1998 Feb; 16(2-3):196-200.
12. 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.
13. 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.
14. 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 TIV inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010-2011. *Vaccine*. 2012 Mar 2;30(11):2024-31.
15. Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2011,” *MMWR* 2011 August 26; 60 (33):1128-1132.7.1.9

## **6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS**

Studies FLU Q-QIV-006, FLU Q-QIV-007 and FLU Q-QIV-003 will be discussed in detail. A brief summary of FLU Q-QIV-(T+)-009 is also provided. Please refer to Section 5 “Review Strategy” for additional information on the overall approach to the review.

### **6.1 FLU Q-QIV-006**

Title: Efficacy Study of GSK Biologicals’ Quadrivalent Influenza Vaccine, GSK2282512A, (FLU Q-QIV) When Administered in Children.

#### **6.1.1 Objectives**

The primary objective of the study was to evaluate the efficacy of Q-QIV in the prevention of RT-PCR positive influenza A and/or B disease presenting as influenza-like illness (ILI) compared to a non-influenza vaccine comparator (Havrix®, Hepatitis A vaccine) in children 3 through 8 years of age.

Secondary objectives of the study are described as follows:

- 1) To evaluate the efficacy of Q-QIV in the prevention of moderate to severe cases of influenza confirmed by RT-PCR, compared to Havrix;

‘Moderate to severe influenza’ was defined as RT-PCR-confirmed ILI with fever > 39°C and/or one of the following symptoms: physician-verified shortness of breath, pulmonary congestion, pneumonia, bronchiolitis, bronchitis, wheezing, croup, or acute otitis media, and/or physician-diagnosed serious extra-pulmonary complication of influenza, including myositis, encephalitis, seizure and/or myocarditis.

- 2) To evaluate the efficacy of Q-QIV (when compared to Havrix) in the prevention of culture-confirmed influenza A and/or B disease due to seasonal influenza strains antigenically matching the vaccine strains. If the preceding objective was achieved, then the study will evaluate the efficacy of Q-QIV in the prevention of culture-confirmed influenza A and/or B disease due to any seasonal influenza strain.
- 3) To describe the immunogenicity (geometric mean titer, seroconversion rate, seroconversion factor and seroprotection rate) of Q-QIV 28 days after completion of vaccination in a subset of subjects; and
- 4) To assess the reactogenicity/safety of Q-QIV in terms of solicited local and general symptoms during 7 days of follow up after each vaccination; unsolicited symptoms during 28 days of follow-up, serious AEs, medically attended adverse events and potential immune-mediated diseases throughout the entire study period.

*Reviewer Comment: In the opinion of this reviewer, vaccine efficacy of FluLaval QIV in the prevention of culture-confirmed influenza A and/or B disease due to all strains and due to vaccine matched strains is an important secondary objective. The results for culture-confirmed influenza, therefore, will be included in the package insert for this product. Although the use of specific disease endpoints, including severe outcomes, may be useful in characterizing the vaccine efficacy of influenza vaccines, CBER did not agree with the GSK definition of ‘moderate to severe influenza’ because the definition aggregates conditions with widely varying degrees of severity. For example, the case definition of ‘moderate to severe influenza’ aggregates wheezing subjects with subjects diagnosed with encephalitis. The protocol did not provide a validated case definition for each of the influenza associated outcomes listed and important clinical outcomes (such as pneumonia) were not adjudicated, limiting the ability to characterize these findings inconsistent and accurate manner. Finally, the definition for ‘moderate to severe influenza’ includes signs and symptoms such as wheezing and shortness of*

*breath which have limited specificity. Please refer to Section 7.1.5 for additional discussion on this issue.*

### **6.1.2 Design Overview**

This trial was a Phase 3, observer blind, randomized, controlled, international and multi-center study of the efficacy of FluLaval QIV, administered intramuscularly in healthy children 3 through 8 years of age. A total of 5200 subjects were enrolled and randomized in a 1:1 ratio to receive either FluLaval QIV (n=2600) or Havrix® (Hepatitis A vaccine) (n=2600). Subjects received one or two doses of vaccine (either FluLaval QIV or Havrix) based on their influenza vaccination status or history of laboratory confirmed H1N1 infection. Bi-weekly, active ILI surveillance began 2 weeks after the day 0 visit until the final ILI follow up contact. All subjects received a diary card, an ILI booklet, and an ILI information sheet to facilitate passive surveillance at the day 0 visit. Subjects with an ILI episode had two additional clinic visits; nasal and throat swab specimens were collected as soon as possible (within 24 hours) of ILI symptom onset. A follow-up ILI contact occurred 15-22 days after ILI onset. Blood samples for immunogenicity testing were obtained at days 0 and 28 for all subjects with a history of vaccination with influenza vaccine, and days 0 and 56 for all subjects not previously vaccinated with influenza vaccine. All subjects were followed for approximately six months.

*Reviewer Comment: The prospective, randomized study design offers controls for biases and allows for active monitoring of disease attack rates and careful tracking of vaccination status.*

*Havrix (Hepatitis A vaccine) was used as a control vaccine to benefit study subjects in the control arm, but it does not protect against influenza; therefore, FLU Q-QIV-006 provides information on the absolute vaccine efficacy of FluLaval QIV. For comparative safety and immunogenicity data on FluLaval QIV compared to a TIV product in children or adults, please refer to studies FLU Q-QIV-003 and FLU Q-QIV-007 (Sections 6.2 and 6.3).*

### **6.1.3 Population**

The study enrolled children 3 through 8 years of age, who were in stable health at the time of first vaccination.

A brief summary of the exclusion criteria follows:

- 1) Child in care, defined as a child who has been placed under the control or protection of an agency, or cared for by foster parents or living in a home care

- 2) Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune modifying drugs within 6 months prior to the vaccine dose. Inhaled and topical steroids were allowed
- 3) History of Guillain-Barré syndrome within 6 weeks of receipt of prior inactivated influenza virus vaccine
- 4) Any known or suspected allergy to any constituent of influenza vaccines (including egg proteins); a history of anaphylactic-type reaction to consumption of eggs; or a history of severe adverse reaction to a previous influenza vaccine
- 5) Fever (temperature  $\geq 38.0^{\circ}\text{C}$  or  $100.4^{\circ}\text{F}$  by any method) at the time of enrollment
- 6) Acute disease (moderate or severe illness) at the time of enrollment
- 7) Any significant disorder of coagulation or treatment with Coumadin derivatives or heparin
- 8) Ongoing aspirin therapy (to avoid potential cases of Reye's syndrome)
- 9) Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination
- 10) Any other condition which, in the opinion of the Investigator, prevents the subject from participating in the study

Other eligibility criteria that may interfere with the immunogenicity evaluation of the vaccine (such as, but not limited to, subjects who received immunoglobulin and/or any blood products within the 3 months preceding the first dose of study) were also listed.

*Reviewer Comment: The eligibility criteria define a healthy population in the 3 through 8 year age group. The external validity of the results of this vaccine efficacy study may be low for special populations excluded from the study, such as immunocompromised persons and pregnant women.*

#### **6.1.4 Study Treatments or Agents Mandated by the Protocol**

Subjects were randomized in a 1:1 ratio to receive either Havrix or FluLaval QIV.



Subjects aged 6 months through 8 years who have received at least one dose of an influenza A vaccine (H1N1) 2009 monovalent vaccine in the past (or had laboratory confirmed H1N1 infection) AND have received two doses of seasonal influenza vaccine separated by at least one month during last season or have received at least one dose prior to last season.

*Reviewer Comment: The definitions of primed and unprimed were prespecified in the protocol and proposed by the Applicant. There is no regulatory definition for the terms “primed and unprimed.”*

### **6.1.5 Sites and Centers**

This study was conducted at fifteen centers across Bangladesh, Dominican Republic, Honduras, Lebanon, Panama, Philippines, Thailand and Turkey

### **6.1.6 Surveillance/Monitoring**

All subjects were followed using active and passive surveillance for approximately six months for evidence of ILI. ILI was defined as the presence of an oral or axillary temperature  $\geq 37.8^{\circ}\text{C}$  in the presence of at least one of the following symptoms on the same day: cough, sore throat, runny nose or nasal congestion.

*Reviewer Comment: The definition for fever occurring with ILI differed from the Grade 1 definition of fever (temperature  $\geq 38.0^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) -  $\leq 38.5^{\circ}\text{C}$  ( $101.3^{\circ}\text{F}$ ) used in the protocol. Using this definition of fever, it is possible that cases of fever associated with RT-PCR positive ILI may be slightly overestimated in this study, although differences between groups will likely not be exaggerated due to the randomized study design.*

Passive ILI surveillance started on day 0; subjects’ parents were instructed to contact the study center within 24 hours after subject became ill with symptoms consistent with ILI. Active surveillance of ILI began 2 weeks after day 0, parents and/or legally acceptable representatives were contacted by telephone every 2 weeks by study staff using a script to ask about the presence of unreported ILI or AEs.

Each ILI reported within seven days of onset was supposed to be evaluated. Nasal and throat swab specimens were to be collected, preferably within 24 hours. Parents or legally acceptable representatives were instructed to complete the ILI booklet for 15 days after ILI onset. The ILI booklet contained questions about the ILI episodes: what signs and symptoms are present (muscle aches, headache, sore throat, runny or stuffy nose, shortness of breath cough, vomiting, diarrhea, chills, and fatigue), if the ILI resulted in a medically attended visit or hospitalization, what medications were administered, if the subject missed school or daycare, and if a parent missed work to care for subject. The parent was also contacted 15-22 days after ILI onset to

confirm that the ILI booklet was completed and would be returned to the study site; information on symptoms, onset and end dates were also collected.

Nasal and throat swabs were collected from subjects for whom ILI was reported no more than seven days after onset. However, details regarding the ILI were still captured in the database. The ILI booklet was used for these subjects. Nasal and throat swabs were tested for influenza using RT-PCR. Cultures were performed on samples positive by RT-PCR.

Blood samples were collected from previously vaccinated subjects on day 0, day 28 and at the end of safety follow visit (ESFU visit, at least 6 months post-vaccination), and from unprimed subjects on day 0, 56 and at the ESFU visit. A subset of subjects (520 from the QIV group and 130 from the Havrix group) was to have their serum samples tested, while the other serum samples were stored. The immunogenicity subset was selected using systematic randomization from a random sample, every fifth subject in the Q-QIV group and every twentieth subject in the Havrix group (by vaccination order) was selected for the immunogenicity subset.

Solicited adverse reactions following vaccination from days 0 to 6 recorded by parent and/or legal guardian on diary card. The solicited local adverse reactions to be followed were pain, redness, and swelling at the injection site. Pain in children younger than 5 years of age was graded in intensity as follows:

- None (Grade 0)
- Mild (minor reaction to touch, Grade 1)
- Moderate (cries / protests on touch, Grade 2),
- Severe (cries when limb is moved / spontaneously painful, Grade 3)

Pain in children 5 years of age and older was graded as follows:

- None (Grade 0)
- Mild (present but not interfering with normal activity, Grade 1)
- Moderate (painful when limb is moved and interferes with daily activity, Grade 2)
- Severe (significant pain at rest, prevents normal activity, Grade 3).

The maximum intensity of redness and/or swelling was scored as follows:

- Grade 0 ( $\leq 20$  mm)
- Grade 1 ( $\geq 20 - \leq 50$  mm)
- Grade 2 ( $\geq 50 - \leq 100$  mm)
- Grade 3 ( $> 100$  mm)

The solicited systemic AEs were monitored in an age appropriate manner. Subjects younger than 5 years of age) were assessed for drowsiness, fever, irritability/fussiness, and loss of appetite. Subjects 5 years of age and older were assessed for fatigue/tiredness, fever, headache, joint pain, muscle aches (widespread or general), shivering (chills), and gastrointestinal



symptoms (nausea, vomiting, diarrhea, and/or abdominal pain). All solicited systemic AEs were graded in intensity as:

- None (Grade 0)
- Mild (present but no effect on normal daily activity, Grade 1)
- Moderate (interferes with normal activity, Grade 2)
- Severe (prevents normal activity, Grade 3).

Fever was recorded as degrees in Centigrade or Fahrenheit and graded as follows:

- Grade 1:  $\geq 38.0^{\circ} \text{C}$  ( $100.4^{\circ} \text{F}$ ) -  $\leq 38.5^{\circ} \text{C}$  ( $101.3^{\circ} \text{F}$ )
- Grade 2:  $\geq 38.5^{\circ} \text{C}$  ( $101.3^{\circ} \text{F}$ ) -  $\leq 39.0^{\circ} \text{C}$  ( $102.2^{\circ} \text{F}$ )
- Grade 3:  $\geq 39.0^{\circ} \text{C}$  ( $102.2^{\circ} \text{F}$ ) -  $\leq 40.0^{\circ} \text{C}$  ( $104^{\circ} \text{F}$ )
- Grade 4:  $>40.0^{\circ} \text{C}$  ( $104^{\circ} \text{F}$ )

Unsolicited AEs that occurred from day 0 to day 27 were recorded by parent and/or legal guardian on the diary card. SAEs and MAEs were monitored throughout the trial. Table 2 describes the schedule of study events for study FLU Q-QIV 006.

**Table 2. Study FLU Q-QIV-006: Schedule of Events**

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Phone <sup>b</sup>
Trial Timelines (Days)	Day 0	Day 28	Day 56	At least 6 months	End of ILI Surveillance
Informed Consent	X				
Inclusion & Exclusion Criteria	X				
Medical History	X				
History- Directed Physical Examination	X				
Blood Sample (BS) <sup>†</sup>	X (BS1)	X	X (BS2)	X <sup>a</sup>	
Vaccination	X	X <sup>a</sup>			
Diary Cards (DC) Provided	X	X <sup>a</sup>			
Diary Cards Collected		X	X <sup>a</sup>		
Passive ILI surveillance	X	X	X		
Active ILI surveillance		X	X		
MAE, SAEs, pIMDs	X	X	X	X	X

<sup>a</sup>Unprimed subjects only

<sup>b</sup>A phone call was performed only if Visit 4 occurred prior to the end of the ILI surveillance period in the country.

Source: Adapted from sBLA 125163/SN 253; CSR, FLU Q-QIV-006, Tables 1-2, page 55-56

### 6.1.7 Endpoints and Criteria for Study Success

The primary (efficacy) endpoint for the study was:

- 1) First occurrence of RT-PCR positive influenza A and/or B disease from a nose and throat swab obtained concurrently with ILI.

The secondary endpoints of the study were:

- 1) First occurrence, during the ILI surveillance period of RT-PCR positive ILI with “moderate to severe influenza.”

Moderate to severe influenza was defined as follows:

- Fever > 39°C and/or one of the following symptoms: physician verified shortness of breath, pulmonary congestion, pneumonia, bronchiolitis, bronchitis, wheezing, croup, or acute otitis media and/or one of the following, physician diagnosed serious extra pulmonary complication of influenza, including myositis, encephalitis, seizure and/or myocarditis
- 2) First occurrence of culture-confirmed influenza A and/or B disease due to influenza strains antigenically similar to those contained in the vaccine
  - 3) First occurrence of culture-confirmed influenza A and/or B disease due to any influenza strains during the influenza surveillance period
  - 4) The vaccine immunogenicity outcome was the serum hemagglutination inhibition (HI) antibody titer against each of the four vaccine influenza strains.
  - 5) Occurrence, intensity and relationship to vaccination of solicited and unsolicited AEs.

### **6.1.8 Statistical Considerations & Statistical Analysis Plan**

Study subjects were randomized in a 1:1 ratio to receive either FluLaval QIV or Havrix. Minimization factors included age subgroups (3 through 4 years and 5 through 8 years), history of influenza vaccination, priming status and country. Randomization was performed using the SAS<sup>®</sup> program --(b)(4)-.

Data was collected in an observer-blind manner. Study vaccines were administered by authorized medical personnel who did not participate in any of the study clinical evaluation.

It was calculated that 194 RT-PCR-confirmed ILI cases due to influenza A and B strains would be needed to demonstrate that the LL of the two-sided 95% CI for the VE is above 30% with 90% power. This calculation was based on the following assumptions: a true vaccine efficacy of 60% (based on 3 literature reviews); the influenza virus attack rate of 6% in the comparator group, and that 10% of subjects would be non-evaluable.

Based on this calculation, 5200 subjects (2600 per treatment group) were recruited to reach the required number of cases of RT-PCR positive ILI (194) due to influenza A and B strains. Although the study protocol allowed for a second year of the study if insufficient influenza cases were accrued during the first year of the study, the second year was not required because  $\geq 194$  RT-PCR positive influenza cases were attained in the first year of the study. For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements were not replaced. For a complete discussion of statistical considerations, please refer to the review provided by Dr. Sang Ahnn OBE/Division of Biostatistics/Vaccine Evaluation Branch.

### **6.1.9 Study Population and Disposition**

The study began on December 9, 2010 and the last study visit was on January 9, 2012.

#### **6.1.9.1 Populations Enrolled/Analyzed**

The safety analysis was performed on the Total Vaccinated Cohort (TVC). Immunogenicity analyses were performed on the According To Protocol (ATP) Cohort for Immunogenicity (ATP-i). The efficacy analysis was performed on the ATP Cohort for Efficacy (ATP-e).

These cohorts were defined as follows:

- The TVC included all vaccinated subjects.
- The ATP-i included all subjects for whom assay results were available against at least 1 study vaccine antigen component after vaccination and who were within the maximum intervals allowed as defined in the protocol, and who did not present with a medical condition or product leading to exclusion.
- The ATP-e included all subjects who received the study vaccine per their treatment assignment, and had at least 1 follow up after the first vaccination, and who did not meet any criteria for elimination from the ATP analysis during the study.

##### **6.1.9.1.1 Demographics**

Demographic data for subjects enrolled in study FLU Q-QIV-006 are shown in Table 3.

**Table 3. Study FLU Q-QIV-006: Summary of Demographic Characteristics (ATP Cohort for Efficacy)**

		FLUQQIV N=2376		HAVRIX N=2389	
Characteristics	Parameters	Value (n)	%	Value (n)	%
Age (years) at Entry	Mean	5.4	-	5.4	-
Gender	Female	1158	48.7	1147	48.0
	Male	1218	51.3	1242	52.0
Race/Ethnicity	Asian	1410	59.3	1432	59.9
	White – Arabic/north African heritage	70	2.9	68	2.8
	White – Caucasian/European heritage	54	2.3	51	2.1
	African heritage/African American	2	0.1	6	0.3
	Other	840	35.4	832	34.8

Source: Adapted from sBLA 125163/ SN 253; CSR, FLU Q-QIV 006; page 133

The study enrolled roughly equal numbers of males and females. The majority of subjects enrolled in the study were Asian; White Caucasians comprised less than 5% of study subjects.

*Reviewer Comment: No imbalances in randomization were identified. Although the study population differs from the racial ethnic composition of the U.S. population, no known differences in the safety and efficacy of inactivated influenza vaccination related to racial and/or ethnic factors exist.*

### **6.1.9.1.2 Medical/Behavioral Characterization of the Enrolled Population**

The majority of subjects (90%) had no history of influenza seasonal vaccination in the previous 3 seasons.

*Reviewer Comment: The majority of subjects did not have a history or previous influenza vaccination. In this manner, the study population differed from the U.S. population for whom influenza vaccination is recommended annually. The baseline serostatus of subjects (shown in Table 10) suggests that a good percentage of subjects had been infected with influenza virus in the past. The exact manner by which baseline differences in immunity (acquired by natural influenza infection or by influenza vaccination) impact the safety and immunogenicity results of this study, and the applicability of these results to the U.S. population is uncertain.*

### 6.1.9.1.3 Subject Disposition

Table 4 shows the number of subjects who were vaccinated, the number who completed the study and the number of subjects who were withdrawn from the study.

**Table 4. Study FLU Q-QIV-006: Number of Subjects Withdrawn (TVC)**

Disposition	FluLaval QIV	Havrix	Total
	N (%)	N (%)	N (%)
TVC	2584 (100)	2584 (100)	5168 (100)
Number of subjects completed	2481 (96)	2464 (95)	4945 (96)
Number of subjects withdrawn	103 (4)	120 (5)	223 (4)

Completed=number of subjects who completed last study visit

Source: Adapted from sBLA 125163/254; CSR FLU Q-QIV-006, Table 15, page 129

A small percentage (roughly 5%) of subjects withdrew from the study prematurely. The most common reason for withdrawal was withdrawal of consent not due to an AE (59% of subjects withdrawn). Only three subjects withdrew due to AEs; none of these subjects were withdrawn from the study by the Applicant. Protocol violations rarely occurred.

*Reviewer Comment: Both arms of the study had similar attrition rates. The low overall study attrition rate did not raise concerns with respect to the introduction of bias or study conduct.*

The number of subjects excluded from the TVC for the ATP cohort for efficacy and reasons for exclusion are shown in Table 5. For a detailed description of the cohorts of analysis, please see Section 6.1.10.

**Table 5. Study FLU Q-QIV-006 – ATP Cohort for Efficacy with Reasons for Exclusion From TVC**

Disposition	Total	Havrix	FluLaval QIV
	n (%)	n (%)	n (%)
<b>Total Cohort</b>	<b>5175</b>	<b>2587</b>	<b>2588</b>
Dose not administered, but subject number allocated	7	3	4
<b>TVC</b>	<b>5168 (100)</b>	<b>2584 (100)</b>	<b>2584 (100)</b>
Administration of medication/vaccine forbidden in the protocol	15 (<1)	5 (<1)	10 (<1)
Randomization code broken	2 (<1)	1 (<1)	1 (<1)
Study vaccine dose not administered ATP	137 (3)	72 (3)	65 (3)
Protocol violation (eligibility criteria)	3 (< 1)	0 (0)	3 (<1)
Noncompliance with vaccination schedule	232 (4)	123 (5)	109 (4)
Essential serologic data missing	3 (< 1)	1 (<1)	2 (<1)
Other	11 (<1)	6 (<1)	5 (<1)
<b>ATP cohort for efficacy</b>	<b>4765 (92)</b>	<b>2376 (92)</b>	<b>2389 (92)</b>

Source: Adapted from sBLA 125163/ SN 253; CSR QIV-006, Tables 15-16, pages 129-30

\*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.

The number of subjects excluded from the TVC for the primary analysis, the ATP cohort for efficacy, was 8%. The most common reason for exclusion was noncompliance with blood sampling/vaccination schedule.

*Reviewer Comment: As the percentage of subjects excluded from the TVC in the ATP cohort for efficacy was greater than 5%, a second analysis based on the TVC was performed to complement the ATP analysis. No major differences in results were found (data not shown).*

The number of subjects excluded from the TVC in the immunosubset for the ATP analysis of immunogenicity and reasons for exclusion are shown in Table 5.

**Table 6. Study FLU Q-QIV-006 – ATP Cohort for Immunogenicity with Reasons for Exclusion from TVC**

Disposition	Total	FluLaval QIV	Havrix
	n (%)	n (%)	n (%)
<b>TVC in the Immunosubset</b>	<b>707 (100)</b>	<b>544 (100)</b>	<b>163 (100)</b>
Administration of medication/vaccine forbidden in the protocol	1 (<1)	1 (<1)	0
Concomitant infection which may influence immune response	2 (<1)	2 (<1)	0
<i>Study vaccine dose not administered ATP</i>	<i>71 (10)</i>	<i>39 (7)</i>	<i>32 (20)</i>
Noncompliance with blood sampling/vaccination schedule	36 (5)	30 (6)	6 (4)
Essential serologic data missing	18 (3)	15 (3)	3 (2)
<b>ATP cohort for immunogenicity</b>	<b>579 (82)</b>	<b>457 (84)</b>	<b>122 (75)</b>

Source: Adapted from sBLA 125163/SN 253, CSR FLU Q-QIV-006, Table 18, Page 131.

A high percentage of subjects was excluded from the TVC to comprise the immunosubset; the most common reasons for exclusion was that the study vaccine dose was not administered according to protocol.

*Reviewer Comment: Since the percentage of vaccinated subjects in the immunogenicity subset excluded was greater than 5%, a second analysis based on the TVC on the immunogenicity subset was performed to complement the ATP analysis. No major differences in results were found (data not shown).*

## 6.1.10 Efficacy Analyses

### 6.1.10.1 Analyses of Primary Endpoint

The study demonstrated the efficacy of FluLaval QIV in the prevention of RT-PCR positive influenza A and/or B disease presenting as ILI when compared to a non-influenza vaccine in children 3 through 8 years of age. The influenza attack rates and vaccine efficacy of FluLaval QIV are shown in the following table.

**Table 7. Study FLU Q-QIV-006 - FluLaval QIV: Influenza Attack Rates and Vaccine Efficacy against RT-PCR Positive Influenza in Children 3 through 8 Years of Age (ATP Cohort for Efficacy)**

	N <sup>a</sup>	N <sup>b</sup>	Influenza Attack Rates % (n/N)	Vaccine Efficacy % (95% CI)
FLULAVAL QIV	2,379	58	2.4	55.4 (39.1, 67.3)
HAVRIX	2,398	128	5.3	–

CI = confidence interval; RT-PCR = reverse transcriptase polymerase chain reaction.

<sup>a</sup> ATP cohort for efficacy included subjects who met all eligibility criteria, were successfully contacted at least once post-vaccination, and complied with the protocol specified efficacy criteria.

<sup>b</sup> Number of influenza cases.

Source: Adapted from sBLA 125163/ SN 253, CSR, QIV-006, Table 28, page 139

The lower bound of the 95% CI was > 30%, which met the pre-specified success criterion for demonstration of efficacy.

### 6.1.10.2 Analyses of Secondary Endpoints

Vaccine efficacy of FluLaval QIV against culture-confirmed influenza A and/or B in children 3 through 8 years of age was demonstrated as shown in Table 8.

**Table 8. FLU Q-QIV-006: Influenza Attack Rates and Vaccine Efficacy Against Culture-Confirmed Influenza in Children 3 through 8 Years of Age (ATP Cohort for Efficacy)<sup>a</sup>**

	N <sup>a</sup>	N <sup>b</sup>	Influenza Attack Rates % (n/N)	Vaccine Efficacy % (97.5% CI)
<b>Culture-Confirmed Influenza (Antigenically Matched Strains)</b>				
FLULAVAL QIV	2,379	31	1.3	45.1 (9.3, 66.8)
HAVRIX	2,398	56	2.3	–
<b>All Culture-Confirmed Influenza (Matched, Unmatched, and Untyped Strains)</b>				
FLULAVAL QIV	2,379	50	2.1	55.9 (35.4, 69.9)
HAVRIX	2,398	112	4.7	–

CI = CI; RT-PCR = reverse transcriptase polymerase chain reaction.

<sup>a</sup> ATP cohort for efficacy included subjects who met all eligibility criteria, were successfully contacted at least once post-vaccination, and complied with the protocol specified efficacy criteria.

<sup>b</sup> Number of influenza cases.

Source: Adapted from sBLA 125163/ SN 253, CSR, QIV-006, Tables 30-31, Pages 141-2.



Vaccine efficacy against culture-confirmed influenza due to antigenically matched strains was lower than vaccine efficacy against culture-confirmed influenza due to matched, unmatched and untyped strains. Of 162 culture-confirmed influenza cases, 108 (67%) were antigenically typed (87 matched; 21 unmatched); 54 (33%) could not be antigenically typed [but were typed by RT-PCR and nucleic acid sequence analysis: 5 cases A (H1N1) (5 with Havrix), 47 cases A (H3N2) (10 with FluLaval QIV; 37 with Havrix), and 2 cases B Victoria (2 with Havrix)].

*Reviewer Comment: Typically, influenza vaccines have higher vaccine efficacy against matched influenza vaccine strains. However, in this study, vaccine efficacy against culture confirmed influenza due to antigenically matched strains was lower than vaccine efficacy calculated using other methods (RT-PCR positive influenza and culture-confirmed influenza due to any influenza strain). The decreased efficacy noted in this analysis may have been due to the difficulties in typing influenza viruses. The methods used for antigenic typing by culture were validated, and found to be suitable for intended use by CBER reviewers. However, influenza viruses have a high mutation rate resulting in the emergence of new strains that differ to varying degrees from the strains used in the seasonal vaccines. This provides challenges in typing viruses. Whether the study has enough strength statistically depends on how much the viruses mutate, how well matched the vaccine is to circulating strains and how severe the season is. As the study was not powered to evaluate the prevention of culture-confirmed influenza due to antigenically matched strains, the clinical significance of this finding is unknown.*

The Applicant defined the term ‘moderate to severe influenza,’ a collection of thirteen adverse outcomes of varying severity, associated with ILI.

*Reviewer Comment: CBER did not agree with the definition proposed by the Applicant for ‘moderate to severe influenza.’ Please refer to Section 6.1.1 for further discussion regarding use of the term ‘moderate to severe’ influenza, as defined by the Applicant.*

The incidence of these influenza associated adverse outcomes (TVC) is shown in Table 9.

**Table 9. Study FLU Q-QIV-006: Incidence of Influenza-Associated Adverse Outcomes in Subjects with RT-PCR-Positive Influenza Like Illness (ILI) from 14 days Post-Vaccination Through the End of ILI Surveillance (TVC)**

<b>Event</b>	<b>Q-QIV N=2584 N (%)</b>	<b>Havrix N=2584 n (%)</b>
Fever (>39°C)	15 (0.6)	50 (2)
Shortness of breath	0	5 (0.2)
Pneumonia	0	3 (0.1)
Bronchitis	1 (0)	1 (0)
Wheezing	1 (0)	1 (0)
Acute Otitis Media	0	1 (0)
Pulmonary Congestion	0	1 (0)
Seizure	0	0
Bronchiolitis	0	0
Croup	0	0
Encephalitis	0	0
Myocarditis	0	0
Myositis	0	0

Source: Adapted from sBLA 125163/ SN 253, CSR FLU Q-QIV-006, Table 35, page 163

As shown in Table 9, fever > 39°C was the only influenza associated adverse outcome observed in > 1% of subjects in the Havrix arm. The risk reduction of fever >102.2°F/39.0°C associated with RT-PCR-positive influenza was 71.0% (95% CI: 44.8, 84.8) based on the ATP cohort for efficacy [FluLaval QIV (n = 12/2,379); Havrix (n = 41/2,398)]. The other pre-specified adverse outcomes had too few cases to calculate a risk reduction.

*Reviewer Comment: Few of the influenza associated adverse outcomes, except for fever, were observed in this study. In the opinion of this reviewer, fever is a frequent clinical manifestation of influenza disease and does not constitute a moderate or severe manifestation of influenza. Pneumonia, however, is commonly considered a severe outcome of influenza disease. As shown in the table above, a slightly higher number of cases of pneumonia appeared to occur in the FluLaval QIV group than the Havrix group. However, this study was not powered to evaluate risk reduction of pneumonia by FluLaval QIV; these findings neither support nor refute the efficacy of FluLaval QIV in the prevention of pneumonia.*

Serum HI antibody levels were measured as a secondary endpoint. Antibody levels were assessed using the percentages of subjects with post-vaccination HI titers ≥ 1:40 and seroconversion rates. The percentage of subjects vaccinated with FluLaval QIV who had post-vaccination HI titers ≥ 1:40 is shown in Table 10 for each influenza strain.

**Table 10. Study FLU Q-QIV-006: Percentage of Subjects with HI titers  $\geq 1:40$**

**(ATP Cohort for Immunogenicity)**

Influenza Strain	N <sup>a</sup>	FluLaval QIV Arm		Havrix Arm	
		Pre-Vaccination (95% CI)	Post-Vaccination <sup>b</sup> (95% CI)	Pre-Vaccination (95% CI)	Post-Vaccination <sup>b</sup> (95% CI)
A/H1N1	457	33.0 (28.7, 37.6)	98.7 (97.2, 99.5)	32 (23, 41)	32 (24, 41)
A/H3N2	457	44.9 (40.2, 49.5)	97.4 (95.5, 98.6)	54 (44, 63)	52 (42, 61)
B/Victoria	457	27.8 (23.7, 32.1)	96.9 (94.9, 98.3)	30 (22, 39)	32 (24, 41)
B/Yamagata	457	34.8 (30.4, 39.4)	98.9 (97.5, 99.6)	39 (30, 48)	39 (30, 48)

<sup>a</sup>N=number of subjects with available results;

<sup>b</sup>Antibody titers were measured 28 days after the last study vaccination Source: Adapted from sBLA 125163/ SN 253; CSR, QIV-006, Table 68, page 207

**Table 11. Study FLU Q-QIV-006: Seroconversion Rates (SCR)<sup>a</sup> for HI titers 28 Days Post-Vaccination (ATP Cohort for Immunogenicity)**

Influenza Strain	N <sup>b</sup>	FluLaval QIV SCR % (95% CI)	Havrix SCR % (95% CI)
A/H1N1	457	96 (94, 98)	1 (0, 5)
A/H3N2	457	84 (81, 88)	2 (0, 6)
B/Victoria	457	93 (90, 95)	3 (1, 7)
B/Yamagata	457	95 (93, 97)	1 (0, 5)

<sup>a</sup> Seroconversion rate was defined for initially seronegative subjects as HI titer  $\geq 1:40$  post-vaccination and for initially seropositive subjects as four fold or greater rise in antibody titer post-vaccination.

<sup>b</sup> Number of subjects with pre and post vaccination results available.

Source: Adapted from sBLA 125163/ SN 253; CSR, QIV-006, Table 67, page 207

The percentage of subjects with post-vaccination HI titer  $\geq 1:40$  was greater than 95% for all four strains and the seroconversion rate was greater than 80% for all four strains.

*Reviewer Comment: HI titers  $\geq 1:40$  and seroconversion rates both appear to overestimate actual vaccine efficacy which was much lower, and casts doubt on the use of 1:40 as a seroprotective tite*

### 6.1.10.3 Subpopulation Analyses

Vaccine efficacy against RT-PCR-confirmed influenza A and/or B disease presenting as ILI in subjects 3 through 4 years of age was lower than vaccine efficacy in subjects 5 through 8 years of age, as shown in the following table.

**Table 12. Study FLU Q-QIV-006: Vaccine Efficacy for Prevention of RT-PCR Positive ILI by Age Group**

Age Group	VE	95% CI
3 through 4 years of age	35.3%	(-1.3;58.6)
5 through 8 years of age	67.7%	(49.7;79.2)

\*VE was based on Cox regression, adjusted for region, and priming status as covariates.

Source: Statistical Review by Dr. Sang Ahnn, OBE/Division of Biostatistics/Vaccine Evaluation Branch

Immunogenicity data by age subgroups did not correlate well with this finding. As shown in Tables 13 and 14, the HI titers as measured by seroconversion rates and percentages of subjects with post-vaccination HI titers  $\geq$  1:40 were similar in the two age cohorts.

**Table 13. Study FLU Q-QIV-006: Percentages of Subjects With HI Titers  $\geq$  1:40 at Day 28 Post-Vaccination by Age (ATP Cohort for Immunogenicity)**

Influenza Strain	3 through 4 years of age		5 through 8 years of age	
	Pre-Vaccination (95% CI)	Post-Vaccination (95% CI)	Pre-Vaccination (95% CI)	Post-Vaccination (95% CI)
A/H1N1	40 (32, 48)	98 (94, 99)	30 (24, 35)	99 (98, 100)
A/H3N2	48 (40, 56)	94 (89, 97)	43 (38, 49)	99 (98, 100)
B/Victoria	24 (17, 31)	96 (92, 99)	30 (25, 36)	97 (95, 99)
B/Yamagata	22 (15, 29)	98 (95, 100)	42 (36, 48)	99 (98, 100)

CI= Confidence Interval; ATP = According To Protocol; HI = hemagglutinin inhibition

Source: Adapted from sBLA 125163/ SN 253; CSR, Q-QIV-006, Table 73, page 216

**Table 14. Study FLU Q-QIV-006: Seroconversion Rate for HI Titers 28 Days after Last Vaccination by Age (ATP Cohort for Immunogenicity)**

Influenza Strain	3 through 4 years of age SCR % (95% CI)	5 through 8 years of age SCR % (95% CI)
A/H1N1	94 (90, 97)	97 (94, 98)
A/H3N2	86 (80, 91)	83 (79, 88)
B/Victoria	93 (88, 97)	93 (89, 96)
B/Yamagata	98 (94, 99)	94 (91, 96)

<sup>a</sup>N=number of subjects with available results;

<sup>b</sup>n=number of subjects with HI titers  $\geq$  40 1/DIL (3 through 4 years of age)

<sup>c</sup>n=number of subjects with HI titers  $\geq$  40 1/DIL (5 through 8 years of age)

Source: Adapted from sBLA 125163/ SN 253; CSR, QIV-006, Table 72, page 215

*Reviewer Comment: As the study lacked statistical power to evaluate efficacy within age subgroups, the clinical significance of these results is unknown. The immunogenicity data by age subgroup did not correlate well with the finding of decreased vaccine efficacy in the younger age group. This information will be included in the FluLaval QIV package insert with appropriate caveats about its interpretation.*

#### **6.1.10.4 Vaccine Efficacy by Gender, Race or County**

Subgroup analyses of efficacy by gender, race, or country (Bangladesh, Dominican Republic, Honduras, Lebanon, Panama, Philippines, Thailand, and Turkey) did not show any substantial differences in vaccine efficacy of FluLaval QIV by genders, race groups, or countries (data not shown).

#### **6.1.11 Safety Analyses**

##### **6.1.11.1 Methods**

The safety analysis was performed on the TVC.

##### **6.1.11.2 Overview of Adverse Events**

Subjects reported local adverse reactions more frequently than systemic adverse reactions.

The percentages of subjects with solicited local adverse reactions occurring within 7 days of vaccination are shown in Table 15.

**Table 15. Study FLU Q-QIV-006: Percentages of Subjects with Solicited Local Adverse Reactions Within 7 Days<sup>a</sup> of First Vaccination in Children 3 through 8 Years of Age (TVC)**

<b>Local Adverse Reaction</b>	<b>FLULAVAL QIV</b>	<b>HAVRIX</b>
	<b>% N=2546</b>	<b>% N=2551</b>
Pain	39	28
Grade 3 Pain	0.9	0.7
Swelling	1	0.3
Grade 3 Swelling	0	0
Redness	0.4	0.2
Grade 3 Redness	0	0

Source: Adapted from sBLA 125163/ SN 253, CSR FLU Q-QIV-006; Table 102; Page 247.

Pain was the most commonly occurring adverse reaction, reported in 39% of FluLaval QIV recipients compared to 28% of Havrix recipients. The occurrence of grade 3 pain was rare. Redness and swelling occurred in  $\leq 1\%$  of subjects; no grade 3 redness or swelling occurred.

The percentages of subjects with individual solicited systemic adverse reactions by age subgroup are shown in the following table.

**Table 16. Study FLU Q-QIV-006: Percentage of Subjects with Solicited Systemic Adverse Reactions Within 7 Days<sup>a</sup> of First Vaccination in Children 3 through 8 Years of Age<sup>b</sup> (TVC)**

	<b>FluLaval QIV</b> %	<b>Havrix</b> %
<b>3 through 4 Years of Age</b>		
	N = 898	N = 895
Loss of appetite	9	8
Irritability	8	8
Drowsiness	8	7
Fever $\geq 100.4^{\circ}\text{F}$ ( $38.0^{\circ}\text{C}$ )	4	4
<b>5 through 8 Years of Age</b>		
	N = 1,648	N = 1,654
Muscle aches	12	10
Headache	11	11
Fatigue	8	7
Arthralgia	6	5
Gastrointestinal symptoms <sup>c</sup>	6	6
Shivering	3	3
Fever $\geq 100.4^{\circ}\text{F}$ ( $38.0^{\circ}\text{C}$ )	3	3

TVC=Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available.

<sup>a</sup>7 days included day of vaccination and the subsequent 6 days.

<sup>b</sup> Solicited systemic adverse reactions were followed in an age-appropriate manner for younger children.

<sup>c</sup>Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

Source: Adapted from sBLA 125163/ SN 253; CSR QIV-006; Tables 102-104; pages 247-251

The incidence of fever  $\geq 39^{\circ}\text{C}$  within 7 days of vaccination in subjects below 5 years of age, was 1.3% in the FluLaval QIV group and 1.1 % in the Havrix group. (overall per dose). No reports of febrile convulsion occurred in subjects assigned to the FluLaval QIV group; one case of febrile convulsion occurred in the Havrix group.

The frequency of unsolicited AEs was similar in both groups (33% for both FluLaval QIV and Havrix). Nasopharyngitis, which was the most commonly reported unsolicited AE in both study arms. Other unsolicited AEs reported by  $\geq 1\%$  of subjects in the FluLaval QIV group were diarrhea, pyrexia, gastroenteritis, upper respiratory tract infection, varicella, cough, and rhinorrhea. The types of unsolicited AEs reported by  $\geq 1\%$  of Havrix recipients were similar. The percentages of grade 3 unsolicited AEs occurring within the 28 day period post-vaccination (TVC) were 1% in the FluLaval QIV arm, compared to 0.8% in the Havrix arm. Unsolicited adverse reactions (i.e., AEs judged by the investigator to be related to vaccination) occurring within 28 days were reported by 1.2% (30/2584) of subjects in the FluLaval QIV arm and 1.4% (37/2584) of subjects in the Havrix arm. Serious adverse events occurring within 28 days of any

vaccination were reported in 0.7% of subjects who received FluLaval QIV, and in 0.2% of subjects who received Havrix.

*Reviewer Comment: The percentage of subjects with any unsolicited AEs occurring within 28 days of vaccination was similar across study arms. In addition, the types of unsolicited AEs observed were consistent with common childhood symptoms and illnesses. These data do not raise a safety concern associated with FluLaval QIV. SAEs rarely occurred within 28 days of vaccination*

### **6.1.11.3 Deaths**

There were two deaths in this study; the study investigators determined that these deaths were not related to the study investigation.

- A 3 year old female drowned (b)(6) days after receiving second dose of FluLaval QIV.
- A 3 year old male drowned (b)(6) days after receiving first dose of Havrix.

*Reviewer Comment: The narratives for these deaths were reviewed. The investigator's conclusion that the deaths were not related to study vaccine appears reasonable.*

### **6.1.11.4 Nonfatal Serious Adverse Events**

An analysis of nonfatal SAEs occurring during the entire study period and occurring within 28 days post-vaccination was performed. Nonfatal SAEs attributed to the vaccine by the study investigator were also evaluated.

During the entire study period, nonfatal SAEs occurred infrequently in both FluLaval QIV and Havrix recipients (1.4-0.9%, respectively). During the 28 days post-vaccination, < 1% of subjects reported nonfatal SAEs in each study group. A slightly higher percentage of nonfatal SAEs were reported by subjects assigned to the FluLaval QIV group (0.7%) than the Havrix group (0.3%), however. The most frequent nonfatal SAE occurring within 28 days of vaccination was pneumonia or bronchopneumonia.

**Table 17. Study FLU Q-QIV-006: Number of Nonfatal Serious Adverse Events Occurring Within 28 Days of Vaccination by Study Group (TVC)**

Preferred Term	FluLaval QIV N=2584	Havrix N=2584
Pneumonia or bronchopneumonia	4	1
Animal bites	3	0
Gastroenteritis or infectious diarrhea	2	1
Bronchitis	2	0
Amebiasis	1	1
Bronchiolitis	1	0
Croup	1	0
Respiratory distress	1	0
Influenza like illness	1	0
Appendicitis	1	0
Herpes zoster	1	0
Urinary tract infection	1	0
Convulsion	1	0
Joint injury	1	0
Dengue fever	0	1
Visceral leishmaniasis	0	1
Tonsillitis	0	1
Optic nerve glioma	0	1
Total	20 (0.7)	7 (0.3)

QIV=quadrivalent

Source: Adapted from sBLA 125163/ SN 253, Table 138, page 308

Only one nonfatal SAE considered by study investigators to be possibly related to vaccination occurred in the FluLaval QIV group. A 7 year old male from Panama was hospitalized on the day of his second vaccination with FluLaval QIV, with symptoms of cough, vomiting, shortness of breath and fever (39.5°C). His white blood cell count 1 day after admission was mildly elevated. He received supportive care, including treatment with antihistamine for possible allergic reaction. The symptoms resolved 10 days later.

*Reviewer Comment: The timing of the nonfatal SAE in the 7 year old subject described raises the possibility that the subject experienced an allergic reaction to the vaccine. Although allergic reactions including anaphylaxis are a known adverse reaction to inactivated influenza vaccines, the high fever in this patient makes alternative etiologies (such as infection due to a bacterial or viral etiology) appear more likely.*



*As an aside, an analysis of the number of subjects with hypersensitivity within two days of vaccination showed that 2 cases of hypersensitivity occurred, one in each treatment group (data not shown).*

*Overall, the low percentage of nonfatal SAEs reported in the FluLaval QIV supports the safety of this product. The diagnoses of nonfatal SAEs reported in two or more subjects in the FluLaval QIV arm, reflect illnesses commonly observed in the population studied.*

#### **6.1.11.5 Potential Immune Mediated Diseases (pIMDs)**

No pIMDs occurred in subjects assigned to the FluLaval QIV arm. The study investigators diagnosed one pIMD, glomerulonephritis, in a recipient of Havrix; the diagnosis was not considered related to vaccination with Havrix.

*Reviewer Comment: The study did not detect an increased association between pIMDs and FluLaval QIV.*

#### **6.1.11.6 Clinical Test Results**

There were no clinical laboratory evaluations in this trial.

#### **6.1.11.7 Dropouts and/or Discontinuations**

No dropouts and/or discontinuations of study participants appear to have occurred due to vaccine-related issues. Two subjects withdrew from the study due to death not related to FluLaval QIV. One non serious AE led to premature discontinuation of a subject assigned to the Havrix group.

#### **6.1.11.8 Conclusions**

- The absolute vaccine efficacy in preventing RT-PCR positive influenza A and/or B disease presenting as ILI was 55%, (LL of 95% CI: 39%). The absolute vaccine efficacy in preventing culture confirmed influenza A and/or B disease presenting as ILI was comparable.
- However, vaccine efficacy against culture confirmed influenza disease due to vaccine matched strains was lower (point estimate 45%; LL of 95% CI was 9%). This finding may have been due to difficulty in typing influenza strains.
- In an exploratory analysis by age, vaccine efficacy against RT-PCR-positive influenza A and/or B disease presenting as ILI in subjects 3 through 4 years of age was lower ( 35%; 95% CI: -1.3, 59) than in subjects 5 through 8 years of age (67.7% ; 95% CI: 49.7, 79.2). As the study lacked statistical power to evaluate efficacy within age subgroups, the clinical significance of these results is unknown.

- No safety concerns associated with FluLaval QIV were identified. Although FluLaval QIV causes increased injection site pain, these reactions were mild. No imbalances in the frequency or severity of solicited or unsolicited AEs or group of AEs were observed. An increase in SAEs or uncommon conditions was not observed.

## 6.2 FLU Q-QIV-003

Title: A Phase 3, double-blind, randomized study to evaluate the immunogenicity and safety of GSK Biologicals' quadrivalent influenza vaccine candidate, GSK2282512A (FLU Q-QIV), compared to GSK Biologicals' trivalent influenza vaccine Fluarix® administered intramuscularly to children "3 to 17" years of age; and to describe the safety and immunogenicity of GSK2282512A in children "6-35 months" of age.

### 6.2.1 Objectives

The primary objective was to test the immunogenic non-inferiority, as measured by HI geometric mean titers (GMTs) and seroconversion rates, for the shared viral strains of FluLaval QIV and TIV Fluarix-VB (B Victoria lineage) and Fluarix YB (B Yamagata lineage) in children 3 through 17 years of age.

The secondary objectives included:

- To test the immunogenic superiority of FluLaval QIV versus Fluarix-VB and Fluarix-YB for the influenza B strain contained in the QIV but not the TIV,
- To describe the immunogenicity of FluLaval QIV compared to Fluarix-VB and Fluarix-YB post-vaccination by GMT, seroconversion rate, mean geometric fold rise and percentage of subjects with HI titers  $\geq 1:40$  post-vaccination and in the age groups 3 through 8 years and 9 through 17 years,
- To describe the immunogenicity of FluLaval QIV in subjects 6 through 35 months of age, and
- To evaluate and describe the reactogenicity and safety of FluLaval QIV, Fluarix-VB, and Fluarix-YB.

*Reviewer Comment: Since the pivotal clinical endpoint study, FLU Q-QIV-006 demonstrated efficacy only in children 3 through 8 years of age, this study provided support for extending use to 9 through 17 year olds by non-inferiority comparisons to a vaccine licensed for use in this age group (Fluarix). The study additionally provided demonstration of immunologic benefit of the additional B strain.*

### 6.2.2 Design Overview

Study FLU Q-QIV-003 was a Phase 3, randomized, partially-blinded, parallel group, multi-center study. A total of 2700 subjects ages 3 through 17 years old were to be enrolled, randomized in a 1:1:1 ratio to receive FluLaval QIV, TIV-VB (Fluarix with influenza B of

Victoria lineage), or TIV-VY (Fluarix with influenza B of Yamagata lineage), and were studied in an observer-blind design. Fluarix-VB contained the influenza B strain recommended by the World Health Organization for the Northern Hemisphere 2010-2011 influenza season. Subjects were stratified by age with a ratio of 1:1 for children 3-8 years and 9-17 years. Minimization factors for treatment allocation included age subgroup (3-4 years and 5-8 years), country, and priming status for children younger than 9 years of age. An additional 300 subjects aged 6-35 months were enrolled and received FluLaval QIV in an open label design. Subjects 6 months-8 years were considered 'primed' if they had received at least one dose of an influenza A/H1N1 2009 monovalent vaccine in the last season or had documented A/H1N1 infection AND had received two doses of seasonal influenza immunizations separated by at least one month during the last season. Subjects 6 months-8 years were considered 'unprimed' if they had not received influenza A/H1N1 2009 monovalent vaccine in the last season or had not had documented A/H1N1 infection, had not received any season influenza immunization in the past, or had received only one dose of vaccine for the first time in the last season. Primed subjects received a single intramuscular injection of study vaccine; Unprimed subjects received two doses: one at day 0 and one at day 28. All subjects 9 through 17 years were considered to be primed and received a single dose of study vaccine regardless of vaccination history.

*Reviewer Comment: At the time that this study was conducted, the TIV formulation of FluLaval was not approved for use in children; therefore, Fluarix was used as the active control vaccine. Fluarix is manufactured by a different process in the Applicant's Dresden facility.*

*It is noted that subjects who had received 2 doses of influenza vaccine the previous year, also needed a history of 2009 H1N1 vaccine or documented history of infection with H1N1 to be considered primed. This may have been because the previous year's vaccine did not contain the 2009 H1N1 strain.*

### **6.2.3 Population**

The study enrolled healthy children age 6 months- 17 years of age at the time of vaccination. Individuals were excluded if they had received seasonal or pandemic influenza vaccine in the previous 6 months, if they had a history of hypersensitivity to a previous dose of influenza vaccine or a history of allergy or reactions likely to be exacerbated by any vaccine component, for acute disease or fever at the time of enrollment, for a history of Guillain Barré syndrome within six weeks of enrollment, for coagulation disorder, for immunodeficiency, or for any condition which, in the opinion of the investigator, prevented the individual from participating in the study.

### **6.2.4 Study Treatments or Agents Mandated by the Protocol**

Vaccine was supplied in single-use, pre-filled syringes; each injection contained a volume of 0.5 mL. Study vaccine was administered into the deltoid muscle of the non-dominant arm if the

muscle size was adequate. In subjects with inadequate muscle mass in the deltoid, generally children younger than 12 months, the vaccine was administered into the anterolateral region of the left thigh.

*Reviewer Comment: The only currently US.-licensed vaccines for use in children 6 through 35 months of age are administered as a 0.25 mL intramuscular dose. (See Fluzone and Fluzone QIV package inserts). In this study, a “full” dose, that is, the dose recommended for use in individuals 3 years of age and older was also used in subjects from 6 through 35 months of age.*

FluLaval QIV contained a total of 60 µg of HA. The vaccine lot numbers used in this study were: DFLHA585A and DFLHA642A. The vaccine contained the three influenza strains recommended by WHO and CDC/CBER for the 2010-2011 influenza season in the Northern Hemisphere and an additional B strain from the lineage not included in the recommendations. FluLaval QIV contained a total of 60 µg of HA, 15 µg of HA from each of the following:

- H1N1 strain: A/California/7/2009 NYMC X-179A
- H3N2 strain: A/Victoria/210/2009 NYMC X-187
- B strain (Victoria lineage): B/Brisbane/60/2008
- B strain (Yamagata lineage): B/Florida/4/2006

The formulation of Fluarix VB was identical to that of Fluarix being marketed in the United States for use in the 2010-2011 influenza season. Fluarix VB contained a total of 45 µg of HA. It included 15 µg of the H1N1 and H3N2 strain described above plus the B/Brisbane/60/2008 strain. Fluarix YB also contained a total of 45 µg of HA including 15 µg of the H1N1 strain, 15 µg of the H3N2 strain, and 15 µg of B/Florida/4/2006.

### **6.2.5 Sites and Centers**

The study was conducted under IND 14466 in 32 centers in five countries: Canada, Mexico, Spain, Taiwan, and USA.

### **6.2.6 Surveillance/Monitoring**

Unprimed subjects younger than 9 years of age were seen in the study clinic on days 0, 28, and 56. Primed subjects younger than 9 years of age and all subjects 9 to 17 years of age were seen in the study clinic on days 0 and 28. All subjects were contacted by telephone for safety follow-up on day 180.

Medical history was obtained prior to vaccination on Day 0. A history-directed physical examination was performed on Day 0 and repeated if necessary at subsequent visits. Body temperature was measured prior to vaccination. A urine pregnancy test was obtained for all females of childbearing potential prior to vaccination; the test must have been negative for the subject to be vaccinated. A urine pregnancy test was also obtained at the Day 28 visit.

Subjects were observed for 30 minutes after vaccination. Diary cards were distributed to the subjects' parent or legal representative after vaccination. The parent or legal representative was instructed on how to complete the diary card and when/how to return the diary card. Parents or legal representatives of subjects younger than 5 years of age were instructed to contact the investigator immediately to report seizure activity or fever  $\geq 39.0^{\circ}\text{C}$  ( $102.2^{\circ}\text{F}$ ) in the two days following vaccination.

Information on solicited adverse reactions was collected for seven days after vaccination (day of vaccination and subsequent six days). The solicited local adverse reactions followed were pain, redness, and swelling at the injection site. The solicited general adverse reactions followed in infants and toddlers (subjects younger than 5 years of age) were drowsiness, fever, irritability/fussiness, and loss of appetite. The solicited general adverse reactions followed in children 5 years of age and older were fatigue/tiredness, fever, headache, joint pain, muscle aches (widespread or general), shivering (chills), and gastrointestinal symptoms (nausea, vomiting, diarrhea, and/or abdominal pain).

Information on unsolicited AEs (AEs) was collected for 28 days after vaccination. AEs were captured using MedDRA terminology.

Information on medically attended AEs, potential immune mediated diseases, and serious AEs was collected during the entire study period.

### **6.2.7 Endpoints and Criteria for Study Success**

The primary endpoint was the HI titer to each of the influenza vaccines. Blood was obtained for immunogenicity assessment on day 0 prior to vaccination and again 28 days post-vaccination: on day 28 for primed subjects and those older than 9 years of age and on day 56 for unprimed subjects younger than 9 years of age.

Serum antibody levels were measured using an in-house assay at GSK Biologicals laboratory. Serum HI was used to calculate GMTs and seroconversion rates.

Secondary endpoints included calculation of the percentage of subjects with post-vaccination HI titers  $\geq 1:40$  and seroconversion factor.

Seroconversion rate (SCR) was defined as the percentage of subjects who have a day 0 HI titer  $< 1:10$  and a post-vaccination HI titer  $\geq 1:40$  or a pre-vaccination titer  $\geq 1:10$  and at least a four fold increase in post-vaccination reciprocal titer. Seroconversion factor was defined as the geometric mean of the within-subject ratios of the post-vaccination reciprocal HI titer to the Day 0 reciprocal HI titer.

HI titers to FluLaval QIV would be considered non-inferior to those of Fluarix VB and Fluarix YB if:

- The UL of the two-sided 95% CI (CI) of the post-vaccination GMT ratio (Fluarix/FluLaval QIV) was  $\leq 1.5$  for the three strains contained in each Fluarix vaccine, and
- The UL of the two-sided 95% CI for the difference in SCR (Fluarix – FluLaval QIV) was  $\leq 10\%$  for the three strains in each Fluarix vaccine.
- Superior HI titers would be demonstrated if the LL of the two-sided 95% CI on the GMT ratio was 1.5 or greater and the LL of the two-sided 95% CI on difference in SCR was 10% or greater.

### **6.2.8 Statistical Considerations & Statistical Analysis Plan**

Study subjects 3 through 17 years of age were randomized in a 1:1:1 ratio to receive FluLaval QIV, Fluarix VB, or Fluarix YB. Subjects in this age group were stratified by age into two cohorts: 3 through 8 years of age and 9 through 17 years of age. Minimizing factors included priming status, country of origin, and age subcohorts of 3 through 4 years of age and 5 through 8 years of age. The comparison of FLU Q QIV to Fluarix VB and Fluarix YB was conducted in a double-blind fashion.

The sample size was calculated to result in 725 evaluable subjects in each treatment group and to obtain an overall power of 90% to achieve the primary objective of non-inferiority.

The study populations were:

- The TVC included all vaccinated subjects for whom data were available. Subjects in this cohort were analyzed by treatment administered.
- The ATP cohort for analysis of safety included all subjects who received at least one dose of the study vaccine to which they were randomized, who had sufficient data for a safety analysis, and who had not received a vaccine forbidden in this protocol.
- The ATP cohort for analysis of immunogenicity included all evaluable subjects (who met entry criteria, complied with protocol procedures and intervals, and had no elimination criteria) for whom data concerning immunogenicity measures were available. The primary analysis of immunogenicity was to be performed using this population.

The statistical analysis of safety was descriptive.

Study subjects 6 through 35 months of age were not stratified and were studied in an open-label, non-randomized manner. The immunogenicity and safety analyses in the 6 through 35 month old, open-label cohort were descriptive.

*Reviewer Comment: The Applicant requested an indication for the use of FluLaval QIV in individuals 3 years of age and older. Infants and young children 6 through 35 months of age were included in this study but were studied in an open-label, non-randomized, uncontrolled fashion. The analysis of immunogenicity in this cohort was descriptive. Therefore, the results in this cohort will only be described briefly in this review.*

### **6.2.9 Study Population and Disposition**

The study was conducted in 32 centers in five countries: Canada, Mexico, Spain, Taiwan, and the United States. The first subject was enrolled on October 1, 2010. The last study visit was July 6, 2011.

#### **6.2.9.1 Populations Enrolled/Analyzed**

A total of 3094 subjects were vaccinated: 932 in the FluLaval QIV arm (3 through 17 years of age), 929 in the TIV-VB arm, 932 in the TIV-YB arm, and 301 in the open-label FluLaval QIV arm for infants and young children 6 through 35 month olds.

##### **6.2.9.1.1 Demographics**

For subjects 3 through 17 years old:

The mean age of subjects in all three arms was 8.9 years; 48% of subjects were females. Most subjects were White Caucasians (63 %), 11% in all three arms were Asians, and 9% were African American.

Most subjects had been primed against influenza; 62% in the FluLaval QIV arm, 63% in the TIV-VB arm, and 64% in the TIV-YB arm had been vaccinated against influenza within the previous three years.

*Reviewer Comment: The baseline demographic characteristics were similar between the three study arms.*

The demographic profiles in the ATP cohort for immunogenicity were comparable to those of the TVC.

For subjects 6-35 months:

The mean age was 21 months, 47.5% of subjects were females and the population was predominantly White Caucasian (68%). In this cohort, 62% of subjects had received a seasonal influenza vaccine in the three previous seasons.

### 6.2.9.1.2 Subject Disposition

The number of subjects vaccinated, completing, or withdrawing from the study is shown in the following table.

**Table 18. Study FLU Q-QIV 003: Study Subject Disposition**

	Subjects 3 through 17 Years of Age			Subjects 3 through 35 Months of Age	Total N(%)
	Q-QIV N(%)	TIV-VB N(%)	TIV-YB N(%)	Q-QIV-I <sup>1</sup> N(%)	
Number of subjects vaccinated	932 (100)	929 (100)	932 (100)	301 (100)	3094 (100)
Number of subjects completing study	894 (96)	889 (96)	902 (97)	275 (91)	2960 (96)
Number of subjects discontinuing prematurely	38 (4)	40 (4)	30 (3)	26 (9)	134 (4)
<b>Reasons for premature discontinuation</b>					
Lost to follow-up	28	36	22	14	100
Consent withdrawn	9	4	7	5	25
Protocol violation	0	0	0	2	2
Non-compliance	1	0	1	0	2
Non-serious adverse event	0	0	0	1	1

<sup>1</sup> Q-QIV-I= open-label, FluLaval QIV arm in infants 3 to 35 months of age  
Source: BLA 125163/ SN 253, CSR Q-QIV 003, Table 16, page 86

As shown in the table above, the majority of subjects (96%) who were vaccinated completed the study. The main reason for premature study discontinuation was loss to follow-up. Of the 100 subjects who were lost to follow-up, 86 had completed their vaccination course. One subject in the infant FluLaval QIV arm discontinued the study prematurely due to an adverse event. Please see Section 6.2.12.7 for more details regarding this subject.

*Reviewer Comment: There percentages of subjects 3 through 17 years of age who discontinued the study prematurely were similar in the three study arms. The number of discontinuations across arms suggests that the study was well conducted.*

Of the 3094 subjects in the TVC, 23 were excluded from the ATP safety cohort. An additional 185 subjects were excluded from the ATP immunogenicity cohort. The reasons for exclusion are shown in the following table.



**Table 19. Study FLU Q-QIV-003: Reasons for Exclusion from the ATP Safety and Immunogenicity Cohorts**

	Subjects 3 through 17 Years of Age			Subjects 3 through 35 Months of Age	Total N (99%)
	Q-QIV N(%)	TIV-VB N(%)	TIV-YB N (%)	Q-QIV-I <sup>1</sup> N (99%)	
<b>TVC</b>	932 (100)	929 (100)	932 (100)	301 (100)	3094 (100)
<b>ATP Cohort for Safety</b>	924 (99)	924 (99)	926 (99)	297 (99)	3071 (99)
Administration of forbidden vaccine	5	2	2	3	12
Vaccine not administered ATP	3	2	4	1	10
Randomization code broken	0	1	0	0	1
<b>ATP Immunogenicity Cohort</b>	878 (94)	871 (92)	878 (94)	259 (86)	2886 (93)
Serological data missing	36	35	32	24	127
Non-compliance with blood sampling schedule	7	11	12	8	38
Non-compliance with vaccination schedule	3	7	4	5	19
Protocol violation	0	0	0	1	1

<sup>1</sup> Q-QIV-I= open-label, FluLaval QIV arm in infants 3 to 35 months of age  
Source: BLA 125163/ SN 253, CSR Q-QIV 003, Table 17, page 88

The majority of subjects were included in the ATP safety cohort (99%). Most (93%) subjects were also included in the ATP immunogenicity cohort, the number of subjects who were excluded and the reasons for exclusion were similar between the four study arms. The main reason for exclusion was missing essential serological data.

*Reviewer Comment: The majority of subjects who were vaccinated were included in both the ATP cohort for safety and the ATP cohort for immunogenicity, suggesting that the study was well conducted.*

### 6.2.10 Analyses of Primary Endpoint(s)

The primary objective was to assess non-inferiority of FluLaval QIV versus TIV in terms of HI antibody GMTs and seroconversion rates for the three strains that were included in each of TIV-VB and TIV-YB in children 3-17 years. Criteria for successfully meeting this objective were if the UL of the two-sided 95% CI for the ratio of GMT of TIV-VB or TIV-YB over Q-QIV vaccine did not exceed 1.5 for each strain and if the UL of the two-sided 95% CI for the difference in seroconversion rate of TIV VB or TIV-YB minus Q-QIV did not exceed 10% for each strain. The results for the primary endpoint are shown in the following table.

**Table 20. Study FLU Q-QIV-003: Comparison of HI Titers for FluLaval QIV versus TIV (TIV-VB and TIV-YB) Using GMTs and Seroconversion Rates at Day 28 after Last Vaccination in Children 3 Through 17 Years of Age: Non-inferiority Analysis (ATP Cohort for Immunogenicity)**

Vaccine Strain Number of Subjects Per Vaccine	Adjusted GMT Ratio TIV/Q-QIV <sup>1</sup>		Difference in Seroconversion Rate (TIV minus Q-QIV)	
	Value	UL 95% CI	Value	UL 95% CI
A/California (H1N1) N TIV= 1747 N Q-QIV= 876	1.15	1.25	1.79	4.77
A/Victoria (H3N2) N TIV= 1746 N Q-QIV= 876	0.99	1.07	-1.36	2.41
B/Brisbane (Victoria) N TIV-VB= 870 N Q-QIV= 790	0.96	1.07	-3.05	1.12
B/Florida (Yamagata) N TIV-YB= 877 N Q-QIV= 876	1.08	1.16	-1.80	2.30

CI = Confidence interval; UL = upper limit; GMT=geometric mean titer

<sup>1</sup>Adjusted GMT Ratio = geometric mean antibody titer adjusted for baseline titer

Source: BLA 125163/ SN 253, CSR Q-QIV 003, Tables 22-27, pages 95-97

Criteria for non-inferiority of FluLaval QIV versus TIV-VB and TIV-YB vaccines in terms of adjusted GMT ratio and seroconversion rates were met for all four strains.

*Reviewer Comment: Non-inferiority of HI titers to the influenza strains in FluLaval QIV and to the corresponding influenza strains in two TIV formulations was demonstrated. Therefore, the primary endpoint for the study was met.*

### 6.2.10.1 Analyses of Secondary Endpoints

The secondary endpoints included evaluation of the superiority of FluLaval QIV versus TIV-VB and TIV-YB for the cross reactive antibody response to the influenza B strain that was not included in each TIV vaccine, using HI antibody GMTs and SCRs. Criteria for successfully meeting this objective were if the LL of the two-sided 95% CI of the adjusted GMT ratio of Q-QIV/TIV-VB or Q-QIV/TIV-YB was greater than 1.5 and the LL of the two-sided 95% CI for the difference in seroconversion rate was greater than 10%. The results are shown in the following table.

**Table 21. Study FLU Q-QIV-003: Comparisons of HI Titers for FluLaval QIV versus TIV (TIV-VB or TIV-YB) in Terms of GMTs at Day 28 after Last Vaccination in Subjects 3 Through 17 Years of Age: Superiority Analysis for Type B Strains (ATP Cohort for Immunogenicity)**

Vaccine Strain Number of Subjects Per Vaccine	Adjusted GMT Ratio <sup>1</sup> (Q-QIV/TIV)		Difference in Seroconversion Rate (Q-QIV minus TIV)	
	Value	LL 95% CI	Value	LL 95% CI
B/Brisbane (Victoria) N TIV-YB= 870 N Q-QIV= 876	3.78 (253.7/67.2)	3.43	44.63 (74.5 - 29.9)	40.35
B/Florida(Yamagata) N TIV-VB= 876 N Q-QIV= 876	2.61 (513.8/196.5)	2.41	33.96 (75.2 – 41.3)	29.55

CI = confidence interval

<sup>1</sup>Adjusted GMT Ratio = Geometric mean antibody titers adjusted for baseline titer  
 Source: BLA 125163/ SN 253, CSR Q-QIV 003, Tables 28-31, pages 99-100

Protocol-specified criteria for superiority of HI titers to influenza B strains in FluLaval QIV versus the cross reactive antibody response to the influenza B in the TIVs were met for both influenza B strains that were not included in the respective TIV.

*Reviewer Comment: The HI antibody response to the influenza B strain included in FluLaval QIV was superior to the cross-reactive antibody response to the influenza B strain from the opposite lineage strain included in the TIV.*

The secondary endpoints also included a description of the immunogenicity of the FluLaval QIV vaccine, TIV-VB and TIV-YB in terms of GMTs and percentage of subjects with HI titers  $\geq 1:40$

at Days 0 and 21. These results are shown in the following table and include results for the open-label FluLaval QIV arm in subjects 6 through 35 months of age (Q-QIV-I arm).

**Table 22. Study FLU Q-QIV-003: GMTs for HI Antibodies 28 Days after Last Vaccination and HI Titer  $\geq 1:40$  in Subjects 3 Through 17 Years of Age<sup>a</sup>**

Strain	Group	Timing	GMT			HI Titer $\geq 1:40$		
			Value	LL 95% CI	UL 95% CI	%	LL 95% CI	UL 95% CI
A/California (H1N1)	Q-QIV	Pre	29.4	26.8	32.2	54.8	51.4	58.1
		Post	362.7	335.3	392.3	96.8	95.4	97.9
	TIV-VB	Pre	32.2	29.4	35.3	57.0	53.6	60.3
		Post	429.1	396.5	464.3	97.4	96.1	98.3
	TIV-YB	Pre	29.1	26.6	31.8	54.4	51.0	57.7
		Post	420.2	388.8	454.0	96.6	95.2	97.7
A/Victoria/ (H3N2)	Q-QIV	Pre	18.1	16.7	19.7	33.7	30.5	36.9
		Post	143.7	134.2	153.9	92.9	91.0	94.5
	TIV-VB	Pre	19.0	17.4	20.6	34.6	31.4	37.9
		Post	139.6	130.5	149.3	92.8	90.8	94.4
	TIV-YB	Pre	19.4	17.8	21.1	37.0	33.8	40.3
		Post	151.0	141.0	161.6	93.3	91.4	94.8
B/Brisbane (Victoria)	Q-QIV	Pre	24.8	22.5	27.3	44.3	41.0	47.7
		Post	250.5	230.8	272.0	95.4	93.8	96.7
	TIV-VB	Pre	25.8	23.5	28.4	46.4	43.1	49.8
		Post	245.4	226.9	265.4	96.3	94.9	97.5
	TIV-YB	Pre	25.8	23.5	28.4	45.6	42.3	49.0
		Post	68.1	61.9	74.9	73.3	70.3	76.2
B/Florida (Yamagata)	Q-QIV	Pre	57.9	52.0	64.4	66.0	62.7	69.1
		Post	512.5	477.5	549.9	99.0	98.1	99.5
	TIV-VB	Pre	58.4	52.6	64.9	67.0	63.8	70.1
		Post	197.0	180.7	214.8	92.4	90.5	94.1
	TIV-YB	Pre	65.9	59.3	73.2	70.9	67.8	73.9
		Post	579.0	541.2	619.3	99.4	98.7	99.8

CI = Confidence interval; <sup>a</sup>ATP Cohort for Immunogenicity; Source: BLA 125163/ SN 253, CSR Q-QIV 003, Tables 32,34, pages 101, 105

The GMTs at baseline were similar in the three arms for subjects 3 through 17 years of age. The post-vaccination GMTs in each arm were considerably higher in all three arms for these subjects. In subjects 6 through 35 months post vaccination GMTs were also higher post-vaccination,

however GMTs and percentage of subjects with HI titers  $\geq 1:40$  were lower in this age cohort compared to older children.

*Reviewer Comment: The post-vaccination GMTs were slightly higher in the TIV-VB and TIV-YB arms than in the FluLaval QIV arm for H1N1 influenza strain, but the post-vaccination GMTs to H3N2 and each influenza B strain were similar. Of note, GMTs post-vaccination were considerably lower after vaccination with FluLaval QIV in children 6 through 35 months compared to vaccination with Q-QIV in children 3 through 17 years of age. FluLaval will be licensed in children 3 years of age and older only.*

The results for seroconversion rates and seroconversion factors are shown in the following table.

Seroconversion factor is defined as the fold increase in serum HI GMTs post-vaccination compared to day 0 (i.e., the geometric mean of the within-subject ratios of the post-vaccination reciprocal HI titer to the pre-vaccination reciprocal HI titer).

**Table 23. Study FLU Q-QIV-003: Post-Vaccination Seroconversion Rates (SCR) and Seroconversion Factor (SCF) in Subjects 6 Months Through 17 Years of Age**

Vaccine Strain	Arm	SCR (%)	95% CI		SCF	95% CI	
			LL	UL		LL	UL
A/California (H1N1)	Q-QIV <sup>1</sup>	84.4	81.8	86.7	12.3	11.3	13.3
	TIV-VB <sup>1</sup>	86.8	84.3	89.0	13.3	12.3	14.4
	TIV-YB <sup>1</sup>	85.5	83.0	87.8	14.4	13.3	15.7
	Q-QIV I <sup>2</sup>	84.9	80.0	89.1	11.9	10.5	13.6
A/Victoria/ (H3N2)	Q-QIV <sup>1</sup>	70.1	66.9	73.1	7.9	7.3	8.6
	TIV-VB <sup>1</sup>	67.8	64.6	70.9	7.4	6.8	8.0
	TIV-YB <sup>1</sup>	69.6	66.5	72.7	7.8	7.2	8.5
	Q-QIV I <sup>2</sup>	73.0	67.1	78.3	10.9	9.6	12.4
B/Brisbane (Victoria)	Q-QIV <sup>1</sup>	74.5	71.5	77.4	10.1	9.2	11.1
	TIV-VB <sup>1</sup>	71.5	68.4	74.5	9.5	8.6	10.4
	TIV-YB <sup>1</sup>	29.9	26.9	33.1	2.6	2.5	2.8
	Q-QIV I <sup>2</sup>	84.6	79.6	88.7	14.6	12.8	16.6
B/Florida (Yamagata)	Q-QIV <sup>1</sup>	75.2	72.2	78.1	8.9	8.1	9.7
	TIV-VB <sup>1</sup>	41.3	38.0	44.6	3.4	3.1	3.6
	TIV-YB <sup>1</sup>	73.4	70.4	76.3	8.8	8.0	9.6
	Q-QIV I <sup>2</sup>	93.8	90.2	96.4	25.0	22.0	28.3

CI= Confidence interval<sup>1</sup>Subjects 3 through 17 years of age

<sup>2</sup>Q-QIV-I= open-label, FluLaval QIV arm in infants 3 through 35 months of age

Source: BLA 125163/ SN 253, CSR Q-QIV 003, Tables 33, 35, pages 103, 106

*Reviewer Comment: Seroconversion rates were similar across all arms in subjects 3 through 17 years of age, except for the cross-reactive antibody response observed in TIV arms that did not contain the influenza B strain being assessed. The seroconversion rate for subjects 6 through 35 months of age who received FluLaval QIV was similar to the seroconversion rate observed in the older cohort of subjects who received FluLaval QIV.*

*Seroconversion factor has not been used as a primary or important secondary endpoint in FDA's evaluation of immune responses to influenza vaccines.*

The percentage of subjects with post-vaccination HI titers  $\geq$  1:40 and the seroconversion rates for the two age subgroups, 3 through 8 years and 9 through 17 years, are shown in the following table. There were 423-424 subjects in each arm in the 3 through 8 year age subgroup, and 447-453 subjects in each arm in the 9 through 17 year age subgroup.

**Table 24. Study FLU Q-QIV-003 Post-Vaccination HI Titers  $\geq$  1:40 and Seroconversion Rates by Age Subgroup (3 through 8 Years and 9 through 17 Years) (ATP Cohort for Immunogenicity)**

Vaccine Strain	Arm	Age Subgroup (Years)	% HI Titer $\geq$ 1:40	95%CI	SCR (%)	95%CI
				LL		LL
A/California (H1N1)	Q-QIV	3-8	95.3	92.8	88.4	85.0
		9-17	98.2	96.6	80.6	76.6
	TIV-VB	3-8	97.2	95.1	92.2	89.2
		9-17	97.5	95.6	81.7	77.8
	TIV-YB	3-8	95.5	93.1	89.6	86.3
		9-17	97.6	95.7	81.7	77.8
A/Victoria/ (H3N2)	Q-QIV	3-8	89.2	85.8	68.8	64.1
		9-17	96.5	94.3	71.3	66.9
	TIV-VB	3-8	92.0	89.0	66.7	62.0
		9-17	93.5	90.8	68.9	64.6
	TIV-YB	3-8	91.7	88.7	70.0	65.4
		9-17	94.7	92.2	69.3	64.8
B/Brisbane (Victoria)	Q-QIV	3-8	93.6	90.9	77.8	73.5
		9-17	97.1	95.1	71.5	67.1
	TIV-VB	3-8	95.8	93.4	77.1	72.8
		9-17	96.9	94.8	66.2	61.6
	TIV-YB	3-8	64.1	59.3	31.4	27.0
		9-17	81.9	59.3	28.5	24.4
B/Florida (Yamagata)	Q-QIV	3-8	98.6	97.0	86.5	82.9
		9-17	99.3	98.1	64.7	60.1
	TIV-VB	3-8	85.1	81.4	42.8	38.0
		9-17	99.3	98.1	39.8	35.3
	TIV-YB	3-8	99.1	97.6	87.7	84.2
		9-17	99.8	98.8	60.0	55.4

CI = Confidence interval

Source: BLA 125163/ SN 253, CSR Q-QIV 003, Supplements 21-22, pages 172-174

*Reviewer Comment: In the FluLaval QIV arm, the percentage of subjects with post-vaccination HI titers  $\geq$  1:40 to each of the four antigens was higher in the older subgroup. However, the seroconversion rates were higher for the A/H1N1 and B/Florida strains in the younger cohort; this was likely due to the higher percentage of subjects with baseline HI titers  $\geq$  1:40 in the 9 to 17 year age group to these strains.*

## 6.2.11 Safety Analyses

### 6.2.11.1 Methods

The analysis of safety was based on the TVC, which included 3094 subjects: 932 of whom received FluLaval QIV, 929 of whom received TIV-VB, 932 of whom received TIV-YB, and 301 subjects 6 through 35 months of age who received FluLaval QIV in an open-label arm.

### 6.2.11.2 Overview of Adverse Events

The percentage of subjects with any adverse event (solicited or unsolicited) reported during the first seven days after vaccination (day of vaccination and subsequent six days) is shown in the following table.

**Table 25. Study FLU Q-QIV-003 – Percentages of Subjects with Any Adverse Reaction (Solicited or Unsolicited) in Seven Days Post-Vaccination (TVC)**

Type of Solicited Adverse Reaction	Q-QIV N=932	TIV-VB N=929	TIV-YB 932	Q-QIV I <sup>1</sup> N=301
Any Solicited Adverse Reaction	77.3	71.6	69.0	74.8
Any Grade 3 Solicited Adverse Reaction	7.6	7.4	6.4	10.3
General Solicited Adverse Reaction	51.9	51.6	50.4	64.1
Grade 3 General Solicited Adverse Reaction	4.4	5.7	4.6	8.6
Any Local Solicited Adverse Reaction	68.9	59.2	58.6	51.8
Grade 3 Local Solicited Adverse Reaction	4.0	2.3	2.8	2.7

<sup>1</sup> Q-QIV-I= open-label, FluLaval QIV arm in infants 3 to 35 months of age  
Source: BLA 125163/ SN 253, CSR Q-QIV 003, Tables 38-39, page 111-112.

In subjects 3 through 17 years of age, the percentages of subjects with any adverse event/reaction and with local adverse events/reactions were slightly higher in the FluLaval QIV arm. The percentages of subjects with Grade 3 adverse events/reactions were less than 10% for all arms for subjects 3 through 17 years of age. The percentages of subjects 6 through 35 months of age with general solicited and unsolicited adverse reactions were higher than in the older age groups, while the percentages with local adverse events/reactions were lower in subjects 6 through 35 months of age.

The percentages of subjects with individual solicited local adverse reactions are shown in the following table.



**Table 26. Study FLU Q-QIV-003 – Percentages of Subjects with Individual Solicited Local Adverse Events (TVC)**

Type of Local Solicited AE	Q-QIV N=932	TIV-VB N=929	TIV-YB 932	Q-QIV I <sup>1</sup> N=301
Pain	70	59	58	50
Grade 3 Pain	3.8	2.3	2.8	2.0
Redness	6	4	4	8
Grade 3 Redness (≥50 mm)	0.1	0	0	0.7
Swelling	7	4	4	6
Grade 3 Swelling (≥50 mm)	0.1	0	0	0.3

<sup>1</sup> Q-QIV-I= open-label, FluLaval QIV arm in infants 3 to 35 months of age  
Source: BLA 125163/ SN 253, CSR Q-QIV 003, Tables 40-, page 114

Pain was the most commonly reported of the local solicited adverse reactions in all four treatment arms. Grade 3 pain was uncommon and reported in less than 4% in any arm. In subjects from 3 through 17 years of age, pain was reported more often in the FluLaval QIV arm than in the TIV arms. However, Grade 3 pain was uncommon in both FluLaval QIV arms. Redness and swelling at the injection site were reported in less than 10% of subjects in any arm and were rarely severe (Grade 3).

*Reviewer Comment: The higher percentage of subjects 3 through 17 years of age with pain in the Q-QIV arm may have been related to the higher antigen content in that arm. The percentage of subjects reporting pain in the FluLaval 6 through 35 months arm was lower and may have been related to difficulties in verbalizing pain.*

The percentages of subjects reporting individual local solicited adverse reactions by age cohort and by vaccine dose are shown in the following table.

**Table 27. Study FLU Q-QIV-003: Percentages of Subjects with Individual Solicited Local Adverse Events in Subjects by Age and Vaccination Dose (TVC)**

Type of Local Solicited AE	3 Through 8 Years of Age									9 Through 17 Years of Age		
	Overall			1st Vaccination			2nd Vaccination			QIV N=45 7	TIV- -VB N=4 58	TIV- YB N=4 61
	QIV N=4 56	TIV- VB N=45 3	TIV- YB N=4 55	QIV N=4 56	TIV- VB N=4 52	TIV- YB N=4 54	QIV N=3 24	TIV- VB N=3 22	TIV- YB N=31 7			
Pain	69	58	53.6	60	49	51	52	47	44	71	60.5	60
Grade 3 Pain	3.3	3.1	3.3	2.0	2.0	2.4	1.9	1.6	1.9	4.4	1.5	2.4
Redness	8.3	5.1	5.1	6.4	3.1	4.2	4.0	3.4	3.2	4.2	3.3	2.8
Grade 3 Redness (≥50 mm)	0	0	0	0	0	0	0	0	0	0.2	0	0
Swelling	7.7	5.7	4.0	6.1	3.5	3.1	3.7	4.7	2.2	6.3	3.1	4.6
Grade 3 Swelling (≥50 mm)	0	0	0	0	0	0	0	0	0	0.2	0	0

Source: BLA 125163/ SN 253, CSR Q-QIV 003, Supplement 62, page 221-224.

Pain was the most commonly reported solicited adverse reaction in both age groups. The incidence of subjects with pain was similar in the younger and older age cohorts in the FluLaval QIV arm. The incidence of pain was slightly higher in the older subjects compared to younger in the TIV arms. The incidence of subjects with pain was higher after QIV than after TIV. The percentage of subjects with Grade 3 pain was similar in all arms and age groups, ranging from 1.9 to 4.4%. Redness at the injection site was reported in almost twice as many subjects 3 through 8 years in the Q-QIV arm compared to subjects 9-17 years in the QIV arm. The incidence of swelling was similar in both age cohorts in the QIV arm. The incidence of subjects with swelling and with redness was slightly higher in the Q-QIV arm than the TIV arms in children 3 through 8 years of age. In general, more local solicited adverse reactions were reported after the first vaccination than the second vaccination in unprimed subjects.

*Reviewer Comment: The percentages of subjects in the Q-QIV arm with individual local solicited adverse reactions were similar in the two age groups except for redness at the injection site, which was reported more commonly in the older cohort. The reason for increased erythema at the injection site in younger children is unclear; it is possible that erythema was more noticeable in younger children who had a smaller muscle mass. However, no substantial differences were noted in the percentages of subjects with swelling at the injection site, which might be expected if local adverse reactions clearly correlated with age and size. In addition, the overall percentages of subjects with erythema were small, and there were no Grade 3 erythema reactions. Therefore, the significance of this finding is unclear.*

The percentages of subjects with individual solicited systemic adverse reactions are shown in the following tables. Different types of individual solicited general adverse reactions were followed in children younger than six years of age and in those six years of age and older.

**Table 28. Study FLU Q-QIV-003 – Percentages of Subjects with Individual Solicited General Adverse Reactions in Subjects Younger than 6 Years of Age (TVC)**

	<b>Q-QIV N=185</b>	<b>TIV-VB N=187</b>	<b>TIV-YB N=189</b>	<b>Q-QIV I<sup>1</sup> N=292</b>
Irritability	32	23.5	25	48
Grade 3 Irritability	1.6	0	1.6	4.8
Drowsiness	25	25	27	35
Grade 3 Drowsiness	0	1.6	0.5	2.4
Loss of appetite	22	22	18.5	32
Grade 3 loss of appetite	0	3.2	1.6	1.7
Fever	8.1	8.6	7.9	9.2
Grade 3 Fever ( $\geq 39^{\circ}\text{C}$ )	1.6	2.7	2.6	2.1

<sup>1</sup> Q-QIV-I= open-label, FluLaval QIV arm in infants 3 to 35 months of age  
 Source: BLA 125163/ SN 253, CSR Q-QIV 003, Table 41, pages 117-121

**Table 29. Study FLU Q-QIV 003: Percentages of Subjects with Individual Solicited General Adverse Reactions in Subjects 6 Years of Age and Older (TVC)**

	<b>Q-QIV N=727</b>	<b>TIV-VB N=725</b>	<b>TIV-YB N=726</b>
Muscle aches	30.5	27	27
Grade 3 Muscle Aches	0.8	0.7	1.2
Fatigue	24	24	24
Grade 3 Fatigue	0.8	1.8	1.1
Headache	23	24	22
Grade 3 Headache	1.1	1.2	1.4
Joint Pain	14	13	11
Grade 3 joint pain	0.6	0.7	0.1
Gastrointestinal	11	11	10
Grade 3 Gastrointestinal	1.2	1.1	0.8
Shivering	7.6	7.0	7.3
Grade 3 Shivering	0.6	1.4	0.6
Fever	3.6	4.6	2.8
Grade 3 Fever ( $\geq 39^{\circ}\text{C}$ )	0.7	1.1	0.3

Source: BLA 125163/ SN 253, CSR Q-QIV 003, Table 42, page 125

The most commonly reported solicited systemic adverse reactions ( $\geq 10\%$  of subjects) in children <6 years of age were irritability, drowsiness, and loss of appetite, and in children 6 through 17 years were muscle aches, fatigue, headache, joint pain, and gastrointestinal symptoms. The incidence of each individual general solicited adverse reaction was similar between subjects in the Q-QIV, TIV-VB, and TIV-YB arms. Of note, no fevers of  $40^{\circ}\text{C}$  or

higher were observed. Grade 3 adverse reactions and high fevers post-vaccination were uncommon.

Information on unsolicited AEs was collected for the 28 days post-vaccination. Unsolicited AEs were reported in a total of 30% of subjects in the FluLaval QIV group, 31% in the TIV-VB group and 29.5% in the TIV-YB group. Of these 4.3% in the Q-QIV group, 4.4% in the TIV-VB and 3.8% in the TIV-YB group were Grade 3 AEs.

In subjects 6 through 35 months of age, unsolicited AEs were reported in 53% of subjects; Grade 3 AEs were reported in 8.0% of subjects.

Individual unsolicited AEs reported in 2% or more of subjects in any study arm are shown in the following table.

**Table 30. Study FLU Q-QIV-003 – Percentages of Subjects with Specific Unsolicited AEs That Occurred at Rate  $\geq$  1% in the FluLaval QIV Arm Within 28 Days Post-Vaccination (TVC)**

Type of Unsolicited AE	Q-QIV N=932	TIV-VB N=929	TIV-YB N=932	Q-QIV <sup>1</sup> N=301
Cough	5.7	4.1	5.3	11.3
Nasopharyngitis	5.2	5.1	4.6	4.7
Upper respiratory tract infection	3.9	3.2	3.5	8.0
Oropharyngeal pain	2.4	2.9	2.6	0.3
Pyrexia	2.0	1.7	1.4	7.0
Headache	1.9	1.4	0.8	0.3
Rhinorrhea	1.8	1.3	2.0	11.0
Vomiting	1.7	1.7	1.9	5.6
Pharyngitis	1.4	0.5	0.6	0.7
Diarrhea	1.2	1.1	0.8	6.6
Bronchitis	1.1	0.8	0.4	0

<sup>1</sup> Q-QIV-I= open-label, FluLaval QIV arm in subjects 6 through 35 months of age  
 Source: BLA 125163/ SN 253, CSR Q-QIV 003, Table 45, pages 132-144

Cough, nasopharyngitis, and upper respiratory infection were the most common unsolicited AEs. There were no individual Grade 3 unsolicited AEs reported in 1% or more of subjects in any arm.

*Reviewer Comment: The rates of unsolicited AEs were similar across vaccine arms for subjects 3 through 17 years of age. The incidence of certain AEs, such as teething, rash, otitis media, and rhinitis were age related and were observed more often in children 6 through 35 months of age than in older subjects. Grade 3 unsolicited AEs were uncommon. The types of unsolicited AEs were consistent with illnesses commonly reported in children.*

The most commonly reported unsolicited AEs that were judged as vaccine-related by study investigators in subjects 3 through 17 years of age were cough (0.9-1.1% of subjects), oropharyngeal pain (0.5-0.6% of subjects), and rhinorrhea (0.4-0.6% of subjects). In the 6 through 35 month age group, the most commonly reported AEs judged as vaccine related were rhinorrhea (4.3%), upper respiratory tract infection (2.0%), and cough (1.7%).

During the entire study period, medically attended visits were reported in 37% in the Q-QIV group, 36% in TIV-VB group and 38% in TIV-YB group. Upper respiratory tract infection was the most frequently reported unsolicited AE with a medically attended visit in all three groups (6.9%, 6.9% and 58.0% respectively for Q-QIV, TIV-VB and TIV-YB). Medically attended AEs were reported in 49% of subjects in the 6-35 month age group; upper respiratory tract infection was the most commonly reported medically attended event and was reported in 13% of subjects.

*Reviewer Comment: The percentages of subjects with vaccine-related unsolicited AEs were small. Medically-attended AEs were reported in approximately one-third of subjects. However, both the individual types of unsolicited AEs judged as vaccine related and of medically-attended AEs were consistent with common childhood illnesses.*

### **6.2.11.3 Deaths**

No deaths were reported during the study.

### **6.2.11.4 Nonfatal Serious Adverse Events**

SAEs were reported in 35 subjects: 3 (0.3%) in the FluLaval QIV arm, 6 (0.6%) in the TIV-VB arm, 5 (0.5%) in the TIV-YB arm, and 7 (2.3%) in the infant FluLaval QIV arm. SAEs in subjects 3 through 17 years of age are shown in the following table.

**Table 31. Study FLU Q-QIV-003: Serious Adverse Events (SAEs) Reported for the Entire Study Period for Subjects 3 through 17 Years by Treatment Arm**

SAE	Q-QIV N=932	TIV-VB N=929	TIV-YB N=932
Gastroenteritis	0	1	1
Pneumonia	0	1	1
Depression	1	1	0
Lymphadenitis	1	0	0
Conjunctivitis	0	0	1
Influenza	0	0	1
Anaphylaxis	0	1	0
Hypersensitivity	0	1	0
Urticaria	0	1	0
Angioedema	0	0	1
Hypertension	1	0	0
Intestinal duct remnant	0	1	0
Hepatobiliary disorder	0	1	0
Head injury	0	1	0
Accidental overdose	1	0	0
Anxiety	0	1	0
Suicidal ideation	0	1	0
Bone fracture	0	0	1
Joint dislocation	0	0	1
Hypoglycemia	0	0	1

Source: BLA 125163/ SN 253, CSR Q-QIV 003, Table 46, pages 146-147

SAEs reported in subjects 6 through 35 months of age were asthma in three subjects, pneumonia in two subjects, and in one subject each: RSV infection, gastroenteritis, febrile seizure, grand mal seizure, and foreign body.

*Reviewer Comment: On analysis of the WUNSOL dataset, SAEs that occurred within 28 days of vaccination by treatment arm were:*

- *FluLaval QIV – depression,*
- *TIV-VB – head trauma with facial fractures and angioedema with conjunctivitis (see description in this review)*
- *TIV-YB – duct remnant with biliary dyskinesia and head injury, and*
- *Infant Q-QIV arm – seizure, febrile seizure, asthma and lobar pneumonia, and RSV infection.*

Three SAEs were judged as vaccine related based on the close temporal association between the event and vaccination.

- A 12 year old male had angioedema and conjunctivitis on day 0, several hours after vaccination with TIV-TB. He was seen by his health care provider two days later and treated with antihistamines and steroids. The symptoms resolved four days after treatment was started.
- A 21 month old healthy female with no history of seizures had a grand mal seizure four hours after vaccination with FluLaval QIV. She was taken to the emergency room, where she was afebrile with a normal physical examination except for a rash on her hands and upper thighs. She was treated with diphenhydramine, and the rash resolved. The primary investigator thought that the rash was not consistent with anaphylaxis. The subject did not receive a second vaccination.
- A 30 month old male had a febrile seizure lasting 15 minutes on day 18 after vaccination with FluLaval QIV. He was taken to the emergency room, where his temperature was 39.2° C. He was treated with ibuprofen. He did not receive a second dose of study vaccine.

*Reviewer Comment: On analysis of the WUNSOL dataset, urticaria was reported within 2 days of receipt of study vaccine in 3 subjects in the Q-QIV arm, none in TIV-VB arm, 1 in TIV-YB arm and none in the infant arm. All AEs of urticarial were mild and resolved in 2 to 11 days. One additional subject in the TIV-VB arm and one in the infant arm had vaccine-related rashes within one day of vaccination. Both of these were mild and resolved. There was no clear increase in the number of subjects with allergic reactions in the Q-QIV arms, which is not surprising since TIV influenza vaccines were the study controls. Two subjects in the infant arms had seizures that were judged as vaccine related. However, one occurred 18 days after vaccination when the subject developed a fever. An association between Q-QIV and seizures in these two infants cannot be ruled out. Of note, no seizures were observed in subjects 3 through 17 years of age who received FluLaval QIV.*

#### **6.2.11.5 Adverse Events of Special Interest (AESI)**

There were two potential immune-mediated diseases. A 7 year old was diagnosed with vitiligo 120 days after vaccination with TIV-VB. A 4 year old was diagnosed with psoriasis 104 days after vaccination with TIV-YB. Neither was judged as vaccine related. Both were ongoing at the end of the study.

*Reviewer Comment: Neither of the potential immune-mediated diseases appears to be vaccine-related.*

### **6.2.11.6 Clinical Test Results**

There were no clinical laboratory tests included in the study.

### **6.2.11.7 Dropouts and/or Discontinuations**

One subject in the 6 through 35 month age group was withdrawn by the parent/legal guardian after a fever (non-serious) that occurred after the subject had completed vaccine dosing.

*Reviewer's comment: In the opinion of this reviewer, the discontinuation due to an AE does not appear to be vaccine related.*

### **6.2.12 Conclusions**

- The results of study FLU Q-QIV 003 provide the support for the effectiveness of FluLaval QIV in individuals 3 through 8 years of age and provide the primary basis for demonstration of immunogenicity (effectiveness) and safety of FluLaval QIV in subjects 9 through 17 years of age.
- The study demonstrated lack of immunologic interference with addition of second B strain in FluLaval QIV, based on demonstration of immunologic noninferiority to strains shared with the TIV comparator vaccine.
- The study additionally demonstrated benefit of the additional B strain, based on demonstration of immunologic superiority of FluLaval QIV to B strains not contained in the TIV comparator vaccine.
- No safety signals were identified in the review of this study. The most common adverse events associated with FluLaval QIV in this study were pain at the injection site for all subjects; drowsiness, irritability and loss of appetite for children 3 to less than 6 years of age; and fatigue, muscle aches and headaches for children 6 to less than 18 years of age. There was no increase in the incidence of unsolicited individual AEs or AEs with a specific organ system; SAEs were uncommon.

### **6.3 FLU Q-QIV-007**

Title: A Phase 3, randomized, double-blind, controlled, multi-country, multi-center study to evaluate the immunogenicity, reactogenicity and safety of GSK Biologicals' quadrivalent influenza vaccine study FLU Q-QIV (GSK2282512A) when administered intramuscularly to adults 18 years of age and older.



### 6.3.1 Objectives

The primary objective of the study was to assess lot-to-lot consistency of three lots of FluLaval QIV based on HI antibody GMTs to all four strains, 21 days after intramuscular vaccination of adults 18 years old.

The secondary objectives of the study are described as follows:

- 1) To assess superior immunogenicity, in terms of HI antibody GMTs of FluLaval QIV compared to TIV-VB with respect to the Yamagata lineage B strain and FluLaval QIV compared to TIV-YB with respect to the Victoria lineage B strain.
- 2) To assess the non-inferior immunogenicity in terms of HI antibody GMTs of FluLaval QIV compared to TIV-VB + TIV-YB for the two A strains  
FluLaval QIV compared to TIV-VB for the B Victoria strain  
FluLaval QIV compared to TIV-YB for the B Yamagata strain
- 3) To assess the immunogenicity of FluLaval QIV at day 21 post-vaccination in two age groups, 18-64 years and  $\geq 65$  years of age.
- 4) To describe the immunogenicity of FluLaval QIV, TIV-VB and TIV-YB in terms of HI GMT, percentage of subjects with HI titers  $\geq 1:40$  at days 0 and 21 and seroconversion rate and seroconversion factor at day 21 for all subjects and for age subgroups (18-64 years and  $\geq 65$  years of age)
- 5) To assess the reactogenicity and safety of the FluLaval QIV and TIV vaccines in terms of solicited local and systemic adverse reactions during 7 days post-vaccination, unsolicited AEs during w21 days post-vaccination, medically attended AEs, SAEs and potential immune mediated diseases during the entire study period.

### 6.3.2 Design Overview

Study FLU Q-QIV-007 was a Phase 3, randomized, double-blind, controlled, multi-country, multi-center study to evaluate the lot consistency, immunogenicity, reactogenicity and safety of GSK Biological's QIV influenza vaccine FluLaval QIV when administered intramuscularly to adults 18 years of age and older. Subjects were stratified by age (18-64 years and  $\geq 65$  years) and then randomized in a 2:2:2:1:1 ratio to one of five treatment arms: three lots of FluLaval QIV, FluLaval VB (influenza B from Victoria lineage), or FluLaval YB (influenza B from

Yamagata lineage). FluLaval VB contained the B strain recommended by the World Health Organization for the Northern Hemisphere 2010-2011 influenza season.

### **6.3.3 Population**

The study enrolled healthy males and non-pregnant females who were 18 years of age and older at the time of vaccination.

Exclusion criteria included the following:

- 1) Prior receipt of any 2010/2011 influenza vaccine;
- 2) History of hypersensitivity to a previous dose of influenza vaccine or a history of allergy or reactions likely to be exacerbated by any vaccine component;
- 3) Receipt of an influenza vaccine 6 months preceding the study or any other vaccine within 30 days before the study;
- 4) History of Guillain-Barré Syndrome within 6 weeks of receipt of prior inactivated influenza virus vaccine;
- 5) Clinically significant chronic disease or uncontrolled chronic illness;
- 6) Acute febrile illness or acute disease at the time of enrollment; and
- 7) Chronic administration of immunosuppressants within 3 months prior,
- 8) Administration of immunoglobulins and/or any blood products within 3 months prior

### **6.3.4 Study Treatments or Agents Mandated by the Protocol**

Study subjects were randomized to receive vaccine from one of three lots of FluLaval QIV, TIV inactivated influenza vaccine containing either B/Victoria (TIV-VB), or B/Yamagata influenza strain (TIV-YB). A brief description of each follows.

- 1) FluLaval QIV shared the same three influenza strains included in TIV-VB (FluLaval TIV) but also included an influenza B strain from a different lineage (Yamagata lineage). Each dose contained 15 µg of each of the following antigens (60 µg total):
  - A/California/7/2009 NYMC X-179 (H1N1),
  - A/Victoria/210/2009 NYMC X-187 (H3N2),
  - B/Brisbane/60/2008 (B strain Victoria lineage)
  - B/Florida/4/2006 (B strain Yamagata lineage)

The vaccine lot numbers for the three lots studied were: DFLHA584A, DFLHA585A, DFLHA586A.

- 2) TIV- VB was the FluLaval formulation marketed during the 2010-2011 influenza season. Each dose of TIV-1 contained 15 µg of each of the following antigens (45 µg total):
  - A/California/7/2009 NYMC X-179 (H1N1)
  - A/Victoria/210/2009 NYMC X-187 (H3N2)
  - B/Brisbane/60/2007 (B strain Victoria lineage)
  
- 3) TIV-YB contained the two influenza A strains recommended for the 2010-2011 influenza season. The influenza B strain in TIV-YB was from a different lineage than the influenza B strain recommended for use during the 2010-2011 season. Each dose of TIV-YB contained 15 µg of each of the following antigens (45 µg total):
  - A/California/7/2009 NYMC X-179 (H1N1),
  - A/Victoria/210/2009 NYMC X-187 (H3N2), and
  - B/Florida/4/2006 (B strain Yamagata lineage)

All three study vaccines were provided as pre-filled syringes with an injectable volume of 0.5 mL. Both formulations of TIV contained 0.50 µg of thimerosal per 5 mL dose. FluLaval QIV -----(b)(4)-----.

### **6.3.5 Sites and Centers**

This study was conducted in 12 centers in Canada, Mexico and the United States.

### **6.3.6 Surveillance/Monitoring**

Subjects were seen at the study site on days 0 and 21. Subjects were contacted by phone on day 180.

A medical history was obtained prior to vaccination on day 0; a physical examination was also performed prior to vaccination. A symptom-directed physical examination was performed at the day 21 if deemed necessary by the investigator. Temperature was assessed prior to vaccination. A urine pregnancy test was obtained for all females of childbearing potential prior to vaccination.

Subjects were observed for 30 minutes after vaccination. Diary cards were distributed; subjects were instructed on how to complete the diary card and asked to return the diary card at the day 21 visit.

Blood samples were drawn from all subjects at days 0 and 21 for immunogenicity analysis.

Information on solicited adverse reactions was collected for seven days after vaccination (day of vaccination and subsequent six days). The solicited local adverse reactions followed were pain, redness, and swelling at the injection site. Pain was graded in intensity as none (Grade 0), mild (present but not interfering with daily activities, Grade 1), moderate (painful when limb is moved and interferes with daily activity, Grade 2), or severe (significant pain at rest that prevents normal activities, Grade 3). The greatest surface diameter of redness and swelling was recorded in millimeters. The maximum intensity of redness and/or swelling was scored as Grade 0 ( $\leq 20$  mm), Grade 1 ( $> 20 - \leq 50$  mm), Grade 2 ( $> 50 - \leq 100$  mm), and Grade 3 ( $> 100$  mm). The solicited systemic AEs monitored were fever, headache, fatigue, gastrointestinal symptoms (nausea, vomiting, diarrhea, and/or abdominal pain), joint pain, muscle aches (generalized / widespread), and shivering/chills. All solicited systemic AEs were graded in intensity as none (Grade 0), mild (present but no effect on normal daily activity, Grade 1), moderate (interferes with normal activity, Grade 2) and severe (prevents normal activity, Grade 3). Fever was recorded as degrees on the Diary Card, and temperature of  $\geq 39.0^\circ\text{C}$  /  $102.2^\circ\text{F}$  was scored as Grade 3.

Information on MAEs, pIMDs, and SAEs were collected for the entire 180 day study period for subjects in the FluLaval QIV and TIV arms.

### **6.3.7 Endpoints and Criteria for Study Success**

The primary endpoint was the serum HI titers against the four influenza vaccine strains at day 21 post-vaccination. The response was measured using GMTs at baseline on day 21. The pre-specified criterion for the demonstration of lot-to-lot consistency was that the limits of the two-sided 95% CI for the geometric mean ratio among the three lots were between 0.67-1.5 for each influenza strain included in the vaccine.

The secondary endpoints and criteria for study success were pre-specified as follows:

- 1) Non-inferiority was demonstrated if the UL of the two-sided 95% CI for the ratio of GMT of TIV-YB vaccine or TIV-VB vaccine over Q-QIV vaccine did not exceed 1.5.
- 2) Immunologic superiority of the unique B strain in FluLaval QIV vaccine was demonstrated if the LL of the 2-sided 95% CI of the adjusted GMT ratio as at least 1.5 for both B strains.

- 3) FluLaval QIV at day 21 post-vaccination was assessed in two age groups, 18-64 years and  $\geq 65$  years of age based on CBER's criteria for immunogenicity which require that a) The LL of the 95% CI for seroconversion rate should be  $\geq 40\%$  in subjects 18-64 years of age or  $\geq 30\%$  in subjects  $\geq 65$  years of age and b) The LL of the 95% CI for seroprotection rate should be  $\geq 70\%$  in subjects 18-64 years of age or  $\geq 60\%$  in subjects  $\geq 65$  years of age.

### **6.3.8 Statistical Considerations & Statistical Analysis Plan**

Treatment allocation at each study site was performed using a central randomization system on the internet (SBIR). The randomization algorithm used a minimization procedure accounting for age (18-64 years or  $\geq 65$  years), previous history of influenza vaccination, country and subject identification number.

The power to meet the primary objective of lot-to-lot consistency was 92.4%.

### **6.3.9 Study Population and Disposition**

The first subject was enrolled on October 1, 2010 and the last study contact was June 28, 2011.

#### **6.3.9.1 Populations Enrolled/Analyzed**

A total of 1707 subjects were randomized and 1703 were vaccinated: 1272 (75%) were vaccinated with Q-QIV, 213 (12.5%) with TIV-VB and 218 (12.8%) with TIV-YB. Of the subjects in the Q-QIV group, 423 were vaccinated with lot 1 of Q-QIV, 424 with lot 2 of Q-QIV, and 425 with lot 3 of Q-QIV.

The primary cohort for the analysis of safety was the TVC. The primary cohort for the analysis of immunogenicity was the ATP cohort for analysis of immunogenicity.

The two major cohorts for analysis of safety and immunogenicity were defined as follows:

- 1) The TVC included all vaccinated subjects.
- 2) The ATP cohort for analysis of immunogenicity essentially included all subjects who were vaccinated who complied with the study procedures and intervals as pre-defined in the protocol and for whom data concerning immunogenicity endpoint measures were available.

#### **6.3.9.1.1 Demographics**

Based on the TVC, the majority of subjects in the study were females (61%). The majority of subjects (60%) were White. Non-white subjects were African American (3%), Asian (1.8%), Native American or Alaskan native (0.4%), Native Hawaiian or Pacific Islander (0.1%), and 34.5% were of other races or ethnicities.

No major differences in gender or race between treatment arms (pooled FluLaval QIV, TIV-VB or TIV-YB) were observed. The demographic profiles for all arms in the ATP cohort for immunogenicity were comparable to those of the TVC (data not shown).

The study was stratified by age. The study enrolled 1129 subjects 18-64 years of age and 532 subjects  $\geq 65$  years of age. Within each age strata (18-64 years and  $\geq 65$  years of age), differences in demographic characteristics were observed. A slightly lower percentage of subjects were female in the older age group (57%, 49%, 51% in the  $\geq 65$  years age group for FluLaval QIV, TIV-VB and TIV-YB arms respectively) compared to the younger age group (64%, 73%, 69% of subjects were female for the FluLaval QIV, TIV-VB and TIV-YB arms, respectively). There were fewer African-American subjects in the older age group than in the younger age group (4.5%, 2.9%, 3.5% African Americans in the 18-64 year group for FluLaval QIV, TIV-VB and TIV-YB arms respectively compared to 0%, 2.9%, 0% in the  $\geq 65$  year age group for FluLaval QIV, TIV-VB and TIV-YB arms respectively).

*Reviewer Comment: Overall, the differences in demographics were relatively small and were unlikely to have resulted in substantial differences in antibody response by age or by cohorts for analysis of safety and immunogenicity.*

#### **6.3.9.1.2 Medical/Behavioral Characterization of the Enrolled Population**

A total of 68.8% of subjects in the TVC had received at least 1 influenza vaccination during the previous three influenza seasons: 69% in the FluLaval QIV arm, 69% in TIV-VB arm, 69.3% in the TIV-YB arm.

*Reviewer Comment: The majority of subjects had been primed against influenza. The percentages of subjects vaccinated in the previous year were similar across all study arms.*

#### **6.3.9.1.3 Subject Disposition**

Of 1703 vaccinated subjects, 97% (n=1655) completed the study. The most common reason for withdrawal from the study was loss to follow up (n=35). Six subjects (<1%) withdrew from the study due to a serious AE. No subjects withdrew due to a non-serious AE or due to protocol violation.

**Table 32. Study FLU Q-QIV 007 – Subject Disposition**

	Q-QIV N (%)	TIV-VB N (%)	TIV-YB N (%)	Total N (%)
Number of Subjects Vaccinated	1272 (100)	213 (100)	218 (100)	1703 (100)
Number of Subjects Completing Study	1243 (98)	207 (97)	205 (94)	1655 (97)
Number of Subjects Withdrawn	29 (2)	6 (3)	13 (6)	48 (3)
<b>Reasons for Withdrawal</b>				
Lost to follow-up*	22	5	11	38
Serious Adverse Event	4	0	2	6
Consent Withdrawn	3	1	0	4
Protocol Violation	0	0	0	0
Non-serious Adverse Event	0	0	0	0

\*Includes subjects who migrated/moved from study area  
Source: BLA 125163/ SN 253, CSR Q-QIV 007, Table 17, page 73

*Reviewer Comment: The percentage of subjects who withdrew from the study was small (3%) and roughly similar across Q-QIV and the TIV arms. The reasons for withdrawal appeared to be unrelated to vaccination or to study conduct. Overall, these results suggest that the study was well conducted with adequate follow-up.*

Additional subjects were excluded from the TVC resulting in the ATP cohorts. The reasons for exclusion from the different cohorts are shown in the following table.

**Table 33. Study FLU Q-QIV-007 - Number of Subjects Included in ATP Cohorts with Reasons for Exclusion from TVC**

	Q-QIV-1	Q-QIV-2	Q-QIV-3	TIV-VB	TIV-YB	Total
<b>TVC</b>	423	424	425	213	218	1703
<b>ATP cohort for analysis of immunogenicity</b>	414	416	416	204	211	1661
<b>Reasons for Exclusion from ATP Cohort for Immunogenicity</b>						
Protocol violation	1	2	2	1	3	9
Noncompliance with blood sampling schedule	1	2	3	2	1	9
Serological data missing	7	4	4	6	3	24

Adapted from BLA 125163/ SN 253 CSR Q-QIV 007, Table 18, page 74

*Reviewer Comment: Less than 5% of subjects from the TVC were excluded from the ATP immunogenicity cohort (97.5%). The number of subjects who were excluded and the reasons for exclusion were similar across study arms.*

### 6.3.10 Immunogenicity Analyses

#### 6.3.10.1 Analyses of Primary Endpoint

The immunogenicity data for lot-to-lot consistency are shown in the following table.

**Table 34. Study FLU Q-QIV-007 –Lot-to-Lot Consistency of FluLaval QIV (Adjusted GMT Ratios of HI antibody at Day 21 for the Maximum Difference among Two Lots of Q-QIV (ATP Cohort for Immunogenicity))**

	Q-QIV GMTs		Adjusted GMT ratio		
	Lot A	Lot B*	Value	LL 95% CI	UL 95% CI
A/California/7/2009 (H1N1)	196	216	0.91	0.76	1.07
A/Victoria/210/2009 (H3N2)	117	128	0.91	0.78	1.06
B/Brisbane/60/2007	180	175	1.03	0.90	1.18
B/Florida/4/2006	411	387	1.06	0.93	1.21

GMT= geometric mean titer; CI = CI; Adjusted GMT=geometric mean antibody titer adjusted for baseline titer

\*Lot A and Lot B refer to the two lots that had the maximum difference in adjusted GMT among three pairwise comparisons of two lots for each strain

Adapted from BLA 125163/ SN 253 CSR Q-QIV 007, Tables 24-27, pages 83-84



The study met the primary objective to demonstrate lot-to-lot consistency of three FluLaval QIV lots for each of the four influenza strains contained in the vaccine. The LL and UL of the two-sided 95% CI on the ratio of the GMTs for the each strain were between 0.67 and 1.5 for the largest pairwise GMT ratio among the three lots.

### 6.3.10.2 Analyses of Secondary Endpoints

The study assessed the superior immunogenicity of FluLaval in terms of HI antibody GMTs compared to TIV-VB and TIV-YB with respect to the non-shared B strain.

FluLaval QIV demonstrated superior immunogenicity in terms of HI antibody GMTs, compared to TIV-VB and TIV-YB with respect to the non-shared B strain as shown in the following table.

**Table 35. Study Q-QIV-007: HI Antibody Responses to FluLaval QIV Compared to TIV for the B strain Not Included in Each TIV Vaccine (Adjusted GMT Ratio at Day 21) (ATP Cohort for Immunogenicity)**

Influenza Strain	Adjusted GMT <sup>a</sup>		Adjusted GMT Ratio <sup>b</sup>		
	Q-QIV	TIV <sup>c</sup>	Value	LL 95% CI*	UL 95% CI*
B/Brisbane/60/2007 (Victoria)	177	73	2.44	2.11	2.83
B/Brisbane/3/2007 (Yamagata)	396	182	2.18	1.90	2.51

\*CI = Confidence Interval; GMT=geometric mean titer; Q-QIV=FluLaval QIV; TIV=Trivalent inactivated influenza vaccine

<sup>a</sup>Adjusted GMT=geometric mean antibody titer adjusted for baseline titer

<sup>b</sup>Adjusted GMT ratio = adjusted GMT ratio of Q-QIV/TIV

<sup>c</sup>Immunogenicity was assessed to the B strain not included in the TIV comparator; the TIV contained either B/Yamagata or B/Victoria.

Adapted from BLA 125163/ SN 253, CSR Q-QIV 007, Tables 28-29, page 85

As shown in the table, the LL of the two-sided 95% CI of the adjusted GMT ratio of Q-QIV/TIV-VB or Q-QIV/TIV-YB was greater than 1.5.

*Reviewer Comment: FluLaval QIV induced a higher HI titer to the influenza B strain contained in the QIV vaccine that is not present in the TIV influenza vaccine. This finding supports the immunologic benefit of FluLaval QIV with respect to the additional B strain.*

Non-inferiority of the antibody response to influenza strains shared by FluLaval QIV and TIV was demonstrated, as shown in the following table.

**Table 36. Study FLU Q-QIV-007: HI Antibody Responses to Q-QIV versus TIV in Terms of Adjusted GMT Ratio at Day 21 by Influenza Strain (ATP Cohort for Immunogenicity)**

Influenza strain	Adjusted GMT <sup>a</sup>		Adjusted GMT Ratio <sup>b</sup>		
	Pooled TIV	Q-QIV	Value	LL 95% CI	UL 95% CI
A/California/7/2009 (H1N1)	160	205	0.78	0.68	0.90
A/Victoria/210/2009 (H3N2)	148	124	1.19	1.05	1.35
B/Brisbane/60/2008 (B Victoria)	133	177	0.75	0.65	0.87
B/Florida/4/2006 (Yamagata)	312	396	0.79	0.69	0.90

GMT=geometric mean titer ; Q-QIV=FluLaval QIV; TIV=Trivalent inactivated influenza vaccine comparator containing either Yamagata or Victoria strain; CI = CI

<sup>a</sup>Adjusted GMT = geometric mean titer adjusted for baseline titer

<sup>b</sup>Adjusted GMT ratio=pooled TIV-VB and TIV-YB over Q-QIV

Source: Adapted from BLA 125163/ SN 254, CSR Q-QIV 007, Table 30-32 page 86-87

As shown in Table 36, non-inferiority of HI antibody responses to the shared influenza strains was demonstrated. The UL of the two sided 95% CI for the adjusted GMT ratio of pooled TIV/Q-QIV, TIV-VB/Q-QIV, and TIV-YB/Q-QIV was less than the protocol-specified criterion of 1.5 for each strain.

*Reviewer Comment: On comparison of the antibody response to the influenza strains in the QIV and TIV formulations, inclusion of a fourth influenza strain in the QIV vaccine does not appear to interfere with immunogenicity to the other strains contained in the vaccine.*

The immunogenicity of FluLaval QIV was assessed in two age groups (18 through 64 years and ≥65 years); the results are shown in the following table.

**Table 37. Study FLU Q-QIV 007- Seroconversion, Percentages of Subjects With a Serum HI Titers  $\geq 1:40$  for HI Antibodies for FluLaval QIV Recipients by Age at Day 21 Post-Vaccination (ATP Cohort for Immunogenicity)**

Strain	Group	Seroconversion				% Subjects With HI $\geq 1:40$		
		Age strata	%	LL 95% CI	UL 95% CI	%	LL 95% CI	UL 95% CI
A/California/7/2009 (H1N1)	Q-QIV	18-64y	79	76	82	98	97	99
		+65 y	65	60	69	85	81	89
A/Victoria/210/2009 (H3N2)	Q-QIV	18-64y	69	66	72	92	90	94
		+65 y	61	56	66	87	84	91
B/Brisbane/60/2008 (Victoria)	Q-QIV	18-64y	67	63	70	97	96	98
		+65 y	31	27	36	95	92	97
B/Florida/4/2006 (Yamagata)	Q-QIV	18-64y	63	60	66	100	99	100
		+65 y	37	32	42	100	99	100

Source: Adapted from sBLA 125163/ SN 253; CSR FLU Q-QIV-007, Tables 33-34, Supplement 17, pages 88-89, 173.

*Reviewer Comment: A lower seroconversion rate to B/Victoria in adults 65 years of age and older may reflect high pre-vaccination antibody in this age group. A post-hoc analysis provided by the Applicant, of seroconversion rate to B/Victoria by influenza vaccination history supports this assertion (data not shown). Overall, the immunogenicity data support lot to lot consistency. The added benefit of the extra B strain in an adult population was demonstrated. These data, taken together with the efficacy data in children, support effectiveness of the vaccine in adults.*

### 6.3.10.3 Subpopulation Analyses

A post-hoc analysis of immunogenicity by gender, race or country did not show any remarkable differences (data not shown).

### 6.3.10.4 Dropouts and/or Discontinuations

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded subjects with missing or non-evaluable measurements.

### 6.3.11 Safety Analyses

#### 6.3.11.1 Methods

The safety assessment was performed on the TVC.

Safety was assessed by collection of information for:

- solicited adverse reactions for days 0-6 post-vaccination;
- unsolicited AEs for days 0-20 post-vaccination; and
- SAEs, withdrawals due to AEs, medically attended visits, potential immune mediated disease and pregnancies for the duration of study participation.

Information on concomitant medication use for AEs was also collected. The analysis of safety was performed on the TVC.

#### 6.3.11.2 Overview of Adverse Events

The overall incidence of subjects reporting any AE within the 7-day post-vaccination period was slightly higher (69%) in the FluLaval QIV arm than in the other treatment arms (61.5% in the TIV-VB arm and 54% in the TIV-YB arm). FluLaval QIV caused more local solicited adverse reactions compared to TIV comparators (60% in FluLaval QIV group, 46% in TIV-VB group and 42% in TIV-YB arm). The types of individual solicited local AEs are shown in the table below.

**Table 38. Study FLU Q-QIV-007: Percentages of Subjects with Individual Solicited Local Adverse Reactions (TVC)**

Type of Local Solicited Adverse Reactions	Q-QIV N=1260	TIV-VB N=208	TIV-YB N=216
Pain	59.5	44.7	41.2
Grade 3 Pain	1.7	1	1.4
Redness	1.7	2.9	1.4
Grade 3 Redness ( $\geq 50$ mm)	0	0	0
Swelling	2.5	1.4	3.7
Grade 3 Swelling ( $\geq 50$ mm)	0	0	0

Q-QIV=FluLaval QIV; TVC=Total Vaccinated Cohort; TIV-VB=TIV, containing B/Victoria strain; TIV-YB=TIV containing B/Yamagata strain

Source: sBLA 125163/ SN 253; CSR FLU Q-QIV-007; Table 46, page 105

The most frequent solicited local adverse reaction was injection site pain in 60% of Q-QIV subjects, 45% of TIV-VB subjects, and 41% of TIV-YB subjects. A small percentage (<1.8%) of these were Grade 3 intensity injection site pain. There was no significant difference in frequency of redness or swelling induced by FluLaval QIV arm compared to TIV.

*Reviewer Comment: A higher percentage of FluLaval QIV vaccinees report injection site pain, likely because FluLaval QIV contains a higher antigen content.*

By contrast, FluLaval QIV induced systemic adverse events similar to the TIV comparators studied, as shown in the following table.

**Table 39. Study FLU Q-QIV-007 – Percentages of Subjects with Individual Solicited Systemic Adverse Events (TVC)**

	<b>Q-QIV N=1260</b>	<b>TIV-VB N=208</b>	<b>TIV-YB N=216</b>
Muscle aches	26.3	25	18.5
Grade 3 Muscle aches	0.8	0.5	1.4
Fatigue	21.5	21.6	17.1
Grade 3 Fatigue	0.8	1.0	1.9
Headache	21.5	19.7	22.7
Grade 3 Headache	0.9	0.5	0
Joint pain	14.8	16.7	14.6
Grade 3 Joint Pain	0.8	1	2.9
Gastrointestinal	9.3	10.1	6.9
Grade 3 Gastrointestinal	0.8	1.9	0.5
Shivering	8.8	7.7	6.0
Grade 3 Shivering	0.6	0.5	0.9
Fever	1.5	0.5	1.4
Grade 3 Fever ( $\geq 39^{\circ}\text{C}$ )	0.7	0	1

Q-QIV=FluLaval QIV; TIV-VB=TIV, containing B/Victoria strain; TIV-YB=TIV containing B/Yamagata strain  
 Source: sBLA 125163/ SN 253; CSR FLU Q-QIV-007; Table 47, 107.

Fatigue, headache and muscle aches were the most commonly reported general solicited adverse reactions. Grade 3 general solicited adverse reactions were reported by less than 1.9 % in all vaccine arms. Fever was uncommon and reported in less than 1.5% in all vaccine arms.

*Reviewer Comment: These data do not raise a safety concern associated with FluLaval QIV compared to TIV comparators studied.*

Similar percentages of subjects reported unsolicited AEs within 21 days post-vaccination in each study arm (19% of FluLaval QIV recipients; 23% of TIV-VB recipients; and 23% of TIV-YB recipients). The following table shows specific unsolicited AEs reported by at least 1% of FluLaval QIV recipients within 21 days post-vaccination.

**Table 40. Study FLU Q-QIV-007: Percentages of Subjects with Specific Unsolicited AEs That Occurred at Rates  $\geq$  1% in FluLaval QIV Arm Within 21 Days Post-Vaccination (TVC)**

Type of Unsolicited AE	Q-QIV N=1272	TIV-VB N=213	TIV-YB N=218
Cough	2.0	2.3	1.8
Oropharyngeal Pain	2.0	2.8	2.3
Nasopharyngitis	1.7	2.8	1.8
Upper respiratory tract infection	1.2	1.9	0.9
Headache	1.1	1.4	0.9

<sup>1</sup>Q-QIV=FluLaval QIV; TIV-VB=TIV containing B/Victoria strain; TIV-YB=TIV containing B/Yamagata strain.  
Source: BLA 125163/253, CSR FLU Q-QIV 007; Table 48, pages 110-116

As shown in the preceding table, the most common unsolicited AEs, reported by a similar percentage of subjects in all study arms, were cough, oropharyngeal pain and nasopharyngitis

No imbalances in Grade 3 unsolicited AEs occurring within 21 days post-vaccination, or MAEs occurring during the entire study period were found (data not shown).

The study did not demonstrate any differences in safety during the 7-day post-vaccination period by FluLaval vaccine lot.

Serious adverse events occurring within 21 days of vaccination were reported in 0.4%, 0%, and 0% of subjects who received FLULAVAL QUADRIVALENT, TIV-1 (B Victoria), or TIV-2 (B Yamagata), respectively.

*Reviewer Comment: These data do not raise a safety concern associated with FluLaval QIV compared to TIV comparators studied.*

### 6.3.11.3 Deaths

During the entire study period, 7 subjects died, 5 (0.4%) in the Q-QIV arm, 2 (0.9%) in the TIV-YB arm, and none in the TIV-VB arm. No deaths were considered related to vaccination.

The following is a description of fatalities occurring in FluLaval QIV recipients.

- 1) Subject –(b)(6), a 76 year old male with past medical history of renal cancer, was diagnosed with diffuse metastatic cancer 58 days post-vaccination. He died from metastatic disease (b)(6) days post-vaccination.
- 2) Subject (b)(6), 48 year old female with multiple cardiovascular risk factors (diabetes mellitus, dyslipidemia, hypertension, angina pectoris), was admitted with diaphoresis and shortness of breath and abdominal pain. She was diagnosed with cardiogenic shock due to myocardial infarction, and died (b)(6) days after vaccination.

- 3) Subject (b)(6), a 77 year old female status post coronary artery bypass graft and hypertension was found deceased at home possibly secondary to heart failure, (b)(6) days post- vaccination.
- 4) Subject(b)(6) , a 44 year old male, was found dead at home due to a stab wound to the chest, (b)(6) days post- vaccination.
- 5) Subject (b)(6), a 79 year old male, was diagnosed with non-small cell lung cancer four months after the dose of vaccine. He opted to discontinue chemotherapy after one dose, and receive radiation therapy alone. He subsequently died approximately 3months after being diagnosed with cancer (7 months post-vaccination).

The following is a description of fatalities occurring in the TIV-YB arm:

- 1) Subject (b)(6) , a 70 year old subject, with a past history of Parkinson's disease, developed fatigue, appetite, respiratory distress approximately 5 weeks post-vaccination. He was diagnosed with cirrhosis of the liver (unknown etiology). He eventually opted for palliative care only, and died at home, (b)(6) days post-vaccination.
- 2) Subject(b)(6) , an 87 year old female subject with a past history of hypertension, had an intertrochanteric fracture of the hip 81 days post-vaccination. She subsequently underwent right hemiarthroplasty. Three weeks post-op, she was found deceased at home,(b)(6)months post-vaccination. The cause of death was attributed by the Investigator to be hypoglycemia as the patient had spent a prolonged period of time in bed not eating.

*Reviewer Comment: In the opinion of the investigators and of this reviewer, none of the deaths appear to be related to study vaccine. No deaths were reported within one month of vaccination. The number of deaths in each study arm was consistent with the randomization ratio.*

#### **6.3.11.4 Nonfatal Serious Adverse Events**

Fifty seven nonfatal SAEs were observed during the entire study period: 2.8% in FluLaval QIV arm, 1.4% in TIV-VB arm and 3.2% in TIV-YB arm. None were considered related to vaccination by the investigator.

Nonfatal SAEs reported in two or more subjects in the FluLaval QIV arm during the entire study are shown in the following table.

**Table 41: Study FLU Q-QIV-007 - Number of Subjects with Nonfatal Serious Adverse Events which Were Reported in Two or More Subjects in Either Treatment Arm, During the Entire Study Period (TVC)**

<b>Nonfatal Serious Adverse Event</b>	<b>Q-QIV N=1272</b>	<b>TIV-VB N=213</b>	<b>TIV-YB N=218</b>
Myocardial Infarction	2	0	0
Urinary Tract Infection	2	0	0
Cerebrovascular Accident	2	0	0
Renal Failure Chronic	2	0	0

Source: Adapted from BLA 125163/ SN 253, CSR FLU Q-QIV 007, Table 51, page 133

*Reviewer Comment: The incidence of nonfatal SAEs was low and was similar among the three treatment arms. There did not appear to be an increase in any individual SAE in this study.*

### **6.3.11.5 Potential Immune Mediated Disease (pIMDs)**

Four subjects reported pIMD in the entire study (FluLaval QIV arm: n=3; TIV-YB: n=1; TIV-VB: n=0).

pIMDs reported in the FluLaval QIV arm were polymyalgia rheumatica (n=2) and Sjogren's syndrome and in the TIV-YB arm was sixth nerve palsy.

*Reviewer Comment: In the opinion of the investigator and this reviewer, these results do not raise concern for a safety signal suggestive of a causal relationship between these pIMDs and FluLaval QIV.*

### **6.3.11.6 Clinical Test Results**

No safety laboratory tests were obtained in this study.

### **6.3.11.7 Dropouts and/or Discontinuations**

Six subjects withdrew from the study prematurely because of an AE. All were withdrawn due to fatal SAEs considered unrelated to vaccination. (See Section 6.12.1.3 for a more detailed discussion of these subjects).

### **6.3.11.8 Conclusions**

- Lot-to-lot consistency, in terms of HI antibody GMT ratio, was demonstrated for three lots of FluLaval QIV.
- Non-inferiority of HI antibody response to influenza strains shared by FluLaval QIV and a TIV comparator was demonstrated in adults.



- Superiority of HI antibody responses induced by FluLaval QIV to the non-shared influenza B strain in a TIV comparator was demonstrated in adults.

#### **6.4 FLU Q-QIV-(T+)-009**

Title: A Phase 3A open-label, single dose study to evaluate the study of immunogenicity and safety of GSK Biologicals' quadrivalent split virion influenza vaccine FLU Q-QIV in adults aged 18 years and older

*Reviewer Comment: This study was conducted at the request of the Canadian regulatory authority and was designed to assess the immunogenicity of a FluLaval QIV formulation which contained thimerosal. The usefulness of the study results of study FLU Q-QIV-(T+)-009 are limited for this license supplement because the study was open-label, uncontrolled, and not randomized. In addition, safety follow-up was only 21 days. Therefore, the study design and results will only be discussed briefly in this review.*

##### **6.4.1 Study Design**

Study FLU Q-QIV-(T+)-009 was a Phase 3, open-label, non-randomized, single center, immunogenicity and safety study of FluLaval QIV in adults 18 years of age and older. The primary objective of the study was to evaluate the immunogenicity of FluLaval QIV in adults 18 years of age and older. Subjects were stratified in a 1:1 ratio by age (18 through 60 years and >60 years).

Subjects received a single 0.5 mL dose of FluLaval QIV administered intramuscularly on day 0. The vaccine contained a total of 60 µg of HA per 0.5 mL dose, which contained the three influenza antigens recommended for the 2011-2012 influenza season plus a second influenza B strain of the different lineage from the recommended influenza B strain for that season. The study vaccine also included --(b)(4)-- thimerosal as a preservative.

Blood was drawn for measurement of antibody response on day 21.

Subjects were seen in the study clinic on days 0 and 21. Information on solicited adverse reactions was collected for four days (day of vaccination and subsequent three days). Solicited local adverse reactions followed were pain, redness, and swelling at the injection site. Solicited general adverse reactions followed were fatigue, headache, muscle pain, chills, joint pain, fever (defined as temperature  $\geq 38.0^{\circ}\text{C}$ ) and potential symptoms of oculorespiratory syndrome (red eyes, facial swelling, cough, chest tightness, difficulty breathing, sore throat, hoarseness, and pain on swallowing). Information on unsolicited AEs, SAEs, and AEs leading to premature study discontinuation were collected from day 0 to day 21.

*Reviewer Comment: The solicited general adverse reactions included symptoms of oculorespiratory syndrome, defined as ocular or respiratory symptoms occurring within 24 hours after TIV administration. The syndrome was associated with FluLaval administration in the 2000-2001 influenza season in Canada. The Applicant attributed it to aggregates in that season's formulation and altered the manufacturing process to decrease or prevent such aggregates.*

The primary endpoint was the antibody response as assessed by HI antibodies against each of the four influenza strains included in the study vaccine. The following parameters and their respective 95% CIs were calculated for each influenza strain as follows:

- Geometric mean titers of HI titers at Days 0 and 21,
- Percentage of subjects with HI titer  $\geq 1:40$  at Days 0 and 21,
- Seroconversion rate, defined as the percentage of subjects with either a pre-vaccination HI titer  $<1:10$  with a post-vaccination HI titer  $\geq 1:40$  or subjects with a pre-vaccination HI titer  $\geq 1:10$  and a four fold or greater increase in post-vaccination titer, and
- Seroconversion factor, defined as the fold increase in serum HI GMTs post-vaccination (on Day 21) compared to Day 0.

The statistical analysis of both immunogenicity and safety were descriptive. There were no criteria for demonstration of immunogenicity.

#### **6.4.2 Study Results**

A total of 112 subjects, 56 in each age cohort (18 through 60 years and  $>60$  years) were enrolled. All 112 subjects completed the study; there were no protocol deviations. The mean age was 54.8 years (median of 60.5 years and range of 22 to 82 years). Fifty-seven percent of subjects were female. The majority of subjects were White (98%).

The seroconversion rate for A/H1N1 was 50.0% for A/H3N2 was 48.2%, for B/Victoria was 33.9%, and for B/Yamagata was 35.7%.

The percentages of adults with HI titers  $\geq 1:40$  were 84% for B/Victoria and 86% for B/Yamagata.

*Reviewer Comment: The lower seroconversion rates may have been related to the high baseline HI titers (pre-vaccination HI titers  $\geq 1:40$  of 79% to 85.7% for the four influenza strains). The overall incidence of solicited and unsolicited AEs during the first four days of the study was 82% in the adults 18 through 60 years cohort and 48% in the adults 60 years and older cohort. The percentages of subjects with any solicited local adverse reaction and with individual solicited local adverse reactions are shown in the following table.*

**Table 42. Study FLU Q-QIV-(T+)-009 – Percentages of Subjects with Solicited Local Adverse Reactions by Age**

	<b>Subjects 18-60 Years of Age N=56</b>	<b>Subjects ≥ 60 Years of Age N=56</b>
Pain	73	34
Redness	2	0
Swelling	2	4

Source: sBLA 125163/ SN 253, CSR for FLU Q-QIV-(T+)-009, Table 18, page 54

No Grade 3 solicited local adverse reactions were reported.

*Reviewer Comment: Although pain was the most commonly reported solicited local adverse reaction in both age cohorts, the percentage of subjects with pain was much lower in subjects 60 years of age or older. This was most likely due to immunosenescence.*

The percentages of subjects with individual solicited general adverse reactions are shown in the following table.

**Table 43. Study FLU Q-QIV-(T+)-009 – Percentages of Subjects with Solicited Systemic Adverse Reactions by Age**

	<b>Subjects 18-60 Years of Age N=56</b>	<b>Subjects ≥ 60 Years of Age N=56</b>
Muscle pain	37.5%	11%
Headache	20%	9%
Fatigue	18%	9%
Sore throat	12.5%	9%
Joint pain	12.5%	5%
Cough	5%	7%
Chills	2%	9%
Red eyes	5%	0%
Chest tightness	0	4%
Facial swelling	0	0
Fever	0	0

Source: Adapted from sBLA 125163/ SN 253, CSR for FLU Q-QIV-(T+)-009, Table 19, page 55.

The most commonly observed solicited general adverse reactions were muscle pain, headache, and fatigue in the adults 18 through 60 years cohort and muscle pain in the 60 years and older cohort. There was one Grade 3 solicited general adverse reaction: fatigue in a subject in the older age cohort.

*Reviewer Comment: The percentage of subjects reporting individual solicited systemic adverse reactions was also lower in the older age cohort. There were no episodes of oculorespiratory syndrome.*

Unsolicited AEs were reported in 23% of subjects 18 through 60 years of age and in 21% of subjects 60 years of age and older. The most frequently reported unsolicited AE in both age groups was upper respiratory tract infection (11% in younger age group and 5% in older cohort). The only other unsolicited AE reported in more than one subjects in either age cohort was nasal congestion, which was reported in two subjects in the 18 to 60 year age group. One unsolicited AE, injection site hemorrhage, was judged as related to study vaccine. One Grade 3 or severe unsolicited AE, arthralgia, was reported.

There were no serious AEs reported during the study, and no subjects withdrew from the study prematurely due to an AE.

*Reviewer Comment: The unsolicited AEs reported in this study were consistent with common illnesses in the adult population. There were no serious adverse events; however, this may have been related to the short (21 day) follow-up.*

### 6.4.3 Conclusions

- This small study provides evidence in adults that the formulation intended for licensure which contains thimerosal, induces HI antibody responses as shown by seroconversion rates ( point estimates ranging from 34%-50%) in a high percentages of subjects who had baseline HI titers > 1:40.
- The study provide some safety data in adults for the formulation intended for licensure which contains thimerosal.

## 7. Integrated Overview of Efficacy

### 7.1 Indication

FluLaval QIV is a vaccine indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and influenza B viruses contained in the vaccine.

#### 7.1.1 Methods of Integration

Four studies were submitted to this BLA for review: Studies FLU Q-QIV-003, FLU Q-QIV-007 and FLU Q-QIV-006 and FLU Q-QIV-(T+)-009. Please refer to Table 1 for a summary of the completed studies submitted to this BLA supplement.

Due to differences in study design and study populations, the pooling of immunogenicity data from individual studies was determined to be of limited value. Studies FLU Q-QIV 003, FLU Q-QIV-006 and FLU Q-QIV-007 had rigorous study designs (randomized, blinded, controlled studies). Study FLU Q-QIV-006 was the only clinical endpoint study (pediatric population); additional immunogenicity and safety data in children were collected in study FLU Q-QIV-003. Studies FLU Q-QIV-007 and FLU Q-QIV-(T+)-009 provided safety and immunogenicity data in an adult population 18 years of age and older, including geriatric subjects. Of these studies, FLU Q-QIV-007 had a rigorous study design (randomized, double-blind, controlled). Study FLU Q-

QIV-(T+)-009, an open label, single group study, provided supportive immunogenicity data in an adult population (18 year of age and older) using the thimerosol added (T+) formulation of FluLaval QIV.

### 7.1.2 Demographics and Baseline Characteristics

The four clinical studies submitted to this application produced a robust database pertaining to the efficacy immunogenicity and safety of FluLaval QIV across gender, age and race.

**Table 44. FluLaval QIV Program: Demographics and Baseline Characteristics of Subjects)**

Study	FLU Q-QIV-006 <sup>a</sup>	FLU Q-QIV-003 <sup>b,c</sup>	FLU Q-QIV-007 <sup>b</sup>	FLU Q-QIV-(T+)-009 <sup>b</sup>
Total # Subjects	4765	2793	1661	112
% Female	48	48	61	57
% White – Caucasian/European heritage	2.2	63	60	98
% African/African-American	0.2	9	3.0	0
% Asian	59	11	1.4	0

<sup>a</sup>ATP cohort for efficacy

<sup>b</sup>ATP cohort for immunogenicity

<sup>c</sup>Demographic data for subjects 3-17 years of age shown.

Source: sBLA 125163/SN 253, CSR FLU Q-QIV-006, Table 20, page 133; CSR FLU Q-QIV-003, Table 19, page 91; CSR FLU Q-QIV-007, Table 20, page 76; CSR FLU Q-QIV-(T+)-009, Table 10, page 47.

The majority of subjects were White in the adult studies FLU Q-QIV-007 and FLU Q-QIV-(T+)-009 and in pediatric study FLU Q-QIV-003. In pediatric study Flu Q-QIV-006, the majority of subjects (60%) were of South East Asian heritage.

The proportion of male and female subjects was balanced across the pediatric studies FLU Q-QIV-003 and FLU Q-QIV-006. The adult studies FLU Q-QIV-007 and FLU Q-QIV-(T+)-009 enrolled more women than men.

Please see Section 6 for more detailed description of demographics for each study.

### 7.1.3 Subject Disposition

Subject attrition rate across all studies in the FluLaval QIV development program was low 3-4% for the pivotal studies. Study FLU Q-QIV-(T+)-009 had a short follow-up period (only 21 days).

The percentage of subjects withdrawn and reasons for withdrawal are shown in the following table.

**Table 45. FluLaval QIV Development Program: Percentage of Subjects Withdrawn and Reasons for Withdrawal (TVC)**

	FLU Q-QIV-003 <sup>a</sup> N (%)	FLU Q-QIV-006 N (%)	FLU Q-QIV-007 N (%)	FLU Q-QIV-(T+)-009 N (%)
Number of subjects vaccinated	2793 (100)	5168 (100)	1703 (100)	112 (100)
Number of subjects completed	2715 (96)	4945 (96)	1655 (97)	112 (100)
Number of subjects withdrawn	108 (4)	223 (4)	48 (3)	0 (0)
<b>Reasons for Withdrawal<sup>d</sup></b>				
Serious Adverse Event	0	2 (0.9)	6 (3)	--
Non-serious Adverse Event	0	1 (0.4)	0	--
Protocol Violation	0	2 (0.9) <sup>c</sup>	0	--
Consent Withdrawal	20 (19)	125 (56)	4 (2)	--
Lost to Follow-up <sup>b</sup>	86 (80)	58 (26)	38 (17)	--
Sponsor study termination	0	0	0	--
Other	2 (2)	35 (16)	0	--

<sup>a</sup>Subjects 3-17 years of age

<sup>b</sup>Includes subjects who moved from study area.

<sup>c</sup>The number of subjects considered in the TVC in FLU Q-QIV-006 excludes subjects from center 84424 as described in Section 6.1.

<sup>d</sup>Percentages shown calculated from the number of subjects withdrawn.

Source: sBLA 125163/SN 253; Module 2.7.3; Table 7, page 41

Discontinuations of study participants due to adverse reactions (serious and non-serious) were rare across all studies; none were vaccine-related. The most common reasons for withdrawal included: withdrawal of consent (not due to adverse reaction) and loss to follow up. Protocol violations were generally uncommon. Study FLU Q-QIV-006 had protocol violation resulting in exclusion of data from one study site (failure to provide Diary Cards to subjects' parents). However, the 45 subjects from this one center represented <1% of the entire study population, and this finding does not significantly impact the results of the study.

The percentage of subjects excluded from the TVC for efficacy analyses (clinical efficacy and immunogenicity) ranged from 0-8%, as shown in the following table.

**Table 46. FluLaval Development Program: Percentages of Subjects Enrolled and Excluded from the TVC for ATP Analyses of Immunogenicity or Efficacy**

	<b>FLU Q-QIV-003 N (%)</b>	<b>FLU Q-QIV-007 N (%)</b>	<b>FLU Q-QIV- (T+)- 009 N (%)</b>	<b>FLU Q-QIV- 006 N (%)</b>
TVC	3094 (100)	1703 (100)	112 (100)	5168 (100)
ATP Cohort for Immunogenicity	2886 (93)	1661 (98)	112 (100)	579 (82) <sup>a</sup>
ATP Cohort for Efficacy	--	--	--	4765 (92)

<sup>a</sup>Immunogenicity data were collected from a subset of subjects enrolled in FLU Q-QIV-006 (n=707); the ATP cohort for immunogenicity for study FLU Q-QIV-006 was calculated from this subset.  
Source: Adapted from sBLA 125163/SN 253; Module 2.7.3; Table 8, page 42

Overall, the percentages of subjects excluded from ATP analyses of immunogenicity or efficacy were slightly higher for pediatric studies; the most common reason for exclusion was noncompliance with vaccination schedule or blood sampling schedule.

The ATP analyses for immunogenicity and efficacy excluded a small percentage of subjects from the TVC, and so these analyses were not repeated on the TVC for any of the four clinical studies included in this application.

#### **7.1.4 Analysis of Primary Endpoints**

##### **Vaccine Efficacy in the Prevention of RT-PCR positive Influenza A and/or B Disease Presenting as Influenza Like Illness**

For the pivotal clinical endpoint study, the primary endpoint evaluated the efficacy of FluLaval QIV in the prevention of RT-PCR positive influenza A and/or B disease presenting as ILI, compared to a non-influenza vaccine control, Havrix, in children 3 through 8 years of age. The study met the pre-defined criteria for demonstration of efficacy (the LL of the 2-sided 95% CI was >30%) as shown in the following table.

**Table 47. FluLaval QIV: Influenza Attack Rates and Vaccine Efficacy Against RT-PCR Positive ILI due to Influenza A and/or B in Children 3 through 8 Years of Age (ATP Cohort for Efficacy)<sup>a</sup>**

	N <sup>a</sup>	N <sup>b</sup>	Influenza Attack Rates % (n/N)	Vaccine Efficacy % (CI)
FLULAVAL QIV	2,379	58	2.4	55.4 (95% CI: 39.1, 67.3)
HAVRIX	2,398	128	5.3	–

CI = Confidence Interval; RT-PCR = reverse transcriptase polymerase chain reaction

<sup>a</sup> ATP cohort for efficacy included subjects who met all eligibility criteria, were successfully contacted at least once post-vaccination, and complied with the protocol specified efficacy criteria.

<sup>b</sup> Number of influenza cases.

Source: Adapted from sBLA 125163/ SN 253, CSR, QIV-006, Table 28, page 139

### **Non-inferiority Immunogenicity to TIV with Respect to Shared Strains, in Children 3 Through 17 Years of Age**

Study FLU Q-QIV-003 demonstrated non-inferiority of FluLaval QIV compared to TIV (in terms of HI antibody GMTs and seroconversion rates) for the three strains included in TIV-VB and TIV-YB, in children 3-17 years of age. The UL of the two-sided 95% CI for the ratio of GMT of TIV-VB or TIV-YB over Q-QIV vaccine did not exceed 1.5 for each strain and the UL of the 2-sided 95% CI for the difference in seroconversion rate of TIV VB or TIV-YB minus Q-QIV did not exceed 10% for each strain.



**Table 48. Study FLU Q-QIV-003 - – Non-inferiority of FluLaval QIV versus TIV Based on GMTs and Seroconversion Rate at Day 28 after Last Vaccination (ATP Cohort for Immunogenicity)**

Vaccine Strain Number of Subjects Per Vaccine	GMT Ratio TIV/Q-QIV		Seroconversion Rate (TIV-Q-QIV)	
	Value	UL 95% CI*	Value	UL 95% CI*
A/California (H1N1) N TIV= 1747 N Q-QIV= 876	1.15	1.25	1.79	4.77
A/Victoria (H3N2) N TIV= 1746 N Q-QIV= 876	0.99	1.07	-1.36	2.41
B/Brisbane (Victoria) N TIV-VB= 870 N Q-QIV= 790	0.96	1.07	-3.05	1.12
B/Florida (Yamagata) N TIV-YB= 877 N Q-QIV= 876	1.08	1.16	-1.80	2.30

<sup>1</sup>CI = Confidence Interval  
Source: BLA 125163/ SN 253, CSR Q-QIV 003, Tables 22-27, pages 95-97.

**Lot-to-Lot Consistency of FluLaval QIV**

Study FLU Q-QIV-007 demonstrated lot-to-lot consistency of three lots of FluLaval QIV (in terms of HI antibody GMTs) for all four strains, 21 days post-vaccination in adults ≥18 years of age. The limits of the two-sided 95% CI on the GMT ratio for each strain (largest pairwise GMT ratio among the 3 lots, taken two at a time) were between 0.67 and 1.5 for each strain.

**Study FLU Q-QIV-(T+)-009**

The primary objective of the study was a yearly re-registrational study in Canada designed to provide descriptive data on the immunogenicity of FluLaval QIV in adults 18 years of age and older. The seroconversion rate for A/H1N1 was 50.0% for A/H3N2 was 48.2%, for B/Victoria was 33.9%, and for B/Yamagata was 35.7%. The low seroconversion rates to both influenza B strains may have been related to high baseline HI titers to these strains. The percentages of adults with HI titers of 1:40 or greater were 84% for B/Victoria and 86% for B/Yamagata.

**7.1.5 Analysis of Secondary Endpoint(s)**

**Prevention of Culture-Confirmed Influenza-Like Illness**

In study FLU Q-QIV-006, FluLaval QIV demonstrated efficacy in the prevention of cultured confirmed ILI due to any seasonal influenza strain (matched, unmatched, drifted) met the criteria that the LL of the 95% CI  $\geq 30\%$  ; the point estimate was 56% (LL 95% CI was 35%). However, vaccine efficacy against culture confirmed influenza disease due to vaccine matched strains was lower (point estimate 45%; LL of 95% CI was 9%). The Applicant attributed this finding to difficulty in typing influenza strains. For additional details, please see Section 6.1.11.2.

### **Prevention of ‘Moderate to Severe’ Influenza**

Study FLU Q-QIV-006 additionally sought to demonstrate vaccine efficacy in the prevention of ‘moderate to severe influenza,’ as defined by the Applicant. The Applicant calculated 73% risk reduction (lower bound 95% CI: 51%) for this endpoint. The term ‘moderate to severe influenza’ included an aggregate of 13 difference diagnoses and symptoms, including (but not limited to): shortness of breath, wheezing, bronchiolitis, myocarditis, encephalitis, seizure and fever  $> 39^{\circ}\text{C}$ . The majority of cases (12/14) termed ‘moderate to severe’ influenza was due to fever  $> 39^{\circ}\text{C}$  associated with ILI. The remaining two cases of lower respiratory infection included reports of nonspecific symptoms and diagnoses such as shortness of breath, wheezing, bronchitis, pneumonia or congestion. Three cases of pneumonia occurred in the Havrix group; 0 cases occurred in the FluLaval QIV arm. The number of cases was too small to calculate risk reduction associated with this outcome. No evidence suggested a decrease in the number of hospitalizations associated with use of FluLaval QIV, although the study was underpowered to evaluate this outcome. For additional details, please refer to Reviewer Comment in Section 6.1.1.1.

### **Superiority of FluLaval QIV Compared to TIV Comparators With Respect to Non-Shared B Strain**

Superiority of the immune response to FluLaval QIV compared to TIV vaccines with respect to the non-shared B strain was evaluated in both children and adults.

In the pediatric study of children 3 through 17 years of age (FLU Q-QIV-003), HI antibody responses induced by FluLaval QIV versus TIV-VB and TIV-YB to the non-shared influenza B strain was assessed in terms of HI antibody GMTs and seroconversion rates. Criteria for successfully meeting this objective were met. The LL of the two-sided 95% CI on GMT ratio of Q-QIV/TIV-VB or Q-QIV/TIV-YB was  $> 1.5$ . The LL of the two-sided 95% CI for the difference in seroconversion rate for B/Victoria or B/Yamagata was  $> 10\%$ .

In adults 18 years of age and older (study FLU Q-QIV-007), FluLaval QIV demonstrated superior HI antibody GMTs, compared to TIV-VB and TIV-YB with respect to the non-shared B strain. The LL of the two-sided 95% CI of the adjusted GMT ratio of Q-QIV/TIV-VB or Q-QIV/TIV-YB was  $> 1.5$ .

Taken together, these data justify the inclusion of a second B strain in FluLaval QIV.

### **Non-inferiority Immunogenicity to TIV with Respect to Shared Strains, in Adults $\geq$ 18 Years of Age**

In the adult study FLU Q-QIV-007, demonstrated non-inferior immunogenicity to TIV with respect to shared influenza strains, demonstrating that the inclusion of a fourth influenza strain in the QIV vaccine does not appear to interfere with immunogenicity to the other strains contained in the vaccine.

#### **7.1.6 Subpopulations**

##### **Efficacy in Children 3 Through 4 Years of Age**

In an exploratory analysis, reduced vaccine efficacy for RT-PCR positive influenza A and/or B disease presenting as ILI, was demonstrated in subjects 3 through 4 years of age (35%; 95% CI -1, 59) when compare to subjects 5 through 8 years of age (68%, 95% CI 50, 79). Although antibody response have been observed in some studies to decrease with decreasing age among very young children, the immune response in 3 to 4 years of age was similar to that observed in 5 to 8 year olds in this study. Since the study was not powered to examine vaccine efficacy by age group, the clinical significance of this finding is unknown.

##### **Immunogenicity in Adults $\geq$ 65 Years of Age**

The immunogenicity of FluLaval QIV in adults  $\geq$  65 years of age was assessed in study FLU Q-QIV-007 based on seroconversion rate and percentage of subjects with post-vaccination HI titers  $\geq$  1:40 to each influenza strain contained in the vaccine. Seroconversion rates to influenza A strain to influenza A strains H3N2 (61%; 95% CI 56, 66) and H1N1 (65%; 95% CI 60, 69) were higher than seroconversion rates to influenza B strains B Victoria (31%; 95% CI 27, 36) and B Yamagata (37%; 95% CI 32, 42) contained in the vaccine.

#### **7.1.7 Persistence of Effectiveness**

Vaccination against seasonal influenza is recommended yearly by the ACIP because of frequent changes in circulating strains. “

##### **7.1.10 Conclusions**

- FluLaval QIV was effective in preventing RT-PCR positive influenza A and/or B disease presenting as ILI in children 3 through 8 years of age.
- FluLaval QIV was effective in preventing cultured confirmed ILI due to any seasonal influenza strain (matched, unmatched, drifted) in children 3 through 8 years of age.

- Lot-to-lot consistency of three lots of FluLaval QIV was demonstrated in adults 18 years of age and older.
- FluLaval QIV demonstrated non-inferior immunogenicity to TIV with respect to shared strains in children 3 through 8 years of age and in adults 18 years of age and older.
- 
- FluLaval QIV demonstrated superior HI antibody responses when compared to TIV vaccines with respect to the non-shared B strain in children  $\geq 3$  years of age and in adults.

## **8. INTEGRATED OVERVIEW OF SAFETY**

### **8.1 Safety Assessment Methods**

The safety of FluLaval QIV was assessed in the clinical studies submitted to this supplement as follows:

- Solicited local and systemic adverse reactions recorded between day 0 and 6 post-vaccination in studies FLU Q-QIV-003, FLU Q-QIV-006 and FLU Q-QIV-007; and between day 0 and 3 post vaccination in FLU Q-QIV-(T+)-009.
- Unsolicited AEs recorded between day 0 and 21 post-vaccination in adult studies FLU Q-QIV-007) and FLU Q-QIV-(T+)-009, and until day 28 post-vaccination in pediatric studies FLU Q-QIV-003 and FLU Q-QIV-006.
- SAEs, pIMDs and MAEs recorded during the entire study period (up to 6 months post-vaccination for studies FLU Q-QIV-003 and FLU Q-QIV-007). In study FLU Q-QIV-006, SAEs, pIMDs and MAEs were recorded up to 6 months post-vaccination, or up to the end of the ILI surveillance period. In study FLU Q-QIV-(T+)-009, SAEs and MAEs were recorded up to 21 days post-vaccination (occurrence of pIMDs was not recorded).

### **8.2 Safety Database**

#### **8.2.1 Studies/Clinical Trials Used to Evaluate Safety**

The integrated analysis of safety by the Applicant included all four studies FLU Q-QIV-006, FLU Q-QIV-003, FLU Q-QIV-007 and FLU Q-QIV-009.

#### **8.2.2 Overall Exposure, Demographics of Pooled Safety Populations**

The Applicant generated a robust safety database for evaluation of FluLaval QIV in subjects across age, gender and race. In the four clinical trials, a total of 5201 subjects received at least one dose of FluLaval QIV as described in the proposed package insert. Of the 5201 subjects, 3817 were children (6 months through 18 years of age) and 1384 were adults (18 years of age

and older). The safety database also included geriatric subjects. Among subjects enrolled in the three Phase 3 studies who received a dose of FluLaval QIV, 397 subjects were 65 years of age or older; 56 subjects enrolled in study FLU Q-QIV-(T+)-009 were 60 years of age or older .

Both males and females were represented in the safety database for FluLaval QIV. Slightly more males were enrolled in pediatric studies FLU Q-QIV-003 and FLU Q-QIV-006, (52% in both studies). A slightly higher percentage of women than men were enrolled in the adult studies FLU Q-QIV-007 and FLU Q –QIV-009 (61%-64%, respectively).

The race of the majority of enrolled subjects varied by study. Subjects in studies FLU Q-QIV-003 and FLU Q-QIV-007 were predominantly White (63%-60%), while subjects enrolled in study FLU Q-QIV-006 were predominantly of South East Asian heritage (60%).

*Reviewer Comment: The safety database included both young and elderly subjects who are at increased risk for complications of influenza infection such as hospitalization and death, in addition to adults between 18 and 65 years of age. Unlike previously licensed vaccines, the safety database for FluLaval QIV predominantly includes young children 3 through 8 years of age. In general, inactivated influenza vaccines have an extensive record of safety in both children and adults. FluLaval TIV in particular has been licensed since 2006; no specific safety signals have been identified through postmarketing surveillance to date. Overall, the pre-licensure safety database may reasonably detect AEs occurring at a frequency of 1 in 1000 or greater in association with FluLaval QIV in persons 3 years of age and older. Both males and females are represented in the safety database. Whites and Asians comprised the majority of subjects enrolled in the studies described in this supplement. Generalizability of the results of the studies included in this supplement to subjects from other races may be limited, although the cumulative experience with inactivated influenza vaccines to date does not suggest that ethnic factors influence vaccine safety and efficacy.*

### **8.2.3 Categorization of Adverse Events**

AEs were reported in the CSRs as Preferred Terms using the MedDRA dictionary. The verbatim terms used by the investigator for the AE were provided in the datasets.

### **8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials**

Pooling of data across clinical trials in the FluLaval QIV clinical development program was determined to be of limited value due to variability in clinical trial designs and age-related differences in immunogenicity of inactivated influenza vaccines.

## 8.4 Safety Results

### 8.4.1 Deaths

Across all studies, less than 1% of subjects enrolled and vaccinated in the FluLaval development program died during the study periods. The following table shows causes of death by subject and study arm.

**Table 49. Deaths in the FluLaval QIV Development Program**

Study	Group	Age at onset (years)/Gender	Preferred Term	Study Day
QIV-007	Q-QIV	79/M	Non small cell lung cancer	(b)(6)
QIV-007	Q-QIV	44/M	Stab wound	(b)(6)
QIV-007	Q-QIV	77/F	Cardiac failure	(b)(6)
QIV-007	Q-QIV	76/M	Metastatic neoplasm	(b)(6)
QIV-007	Q-QIV	48/F	Myocardial infarction	(b)(6)
QIV-006	Q-QIV	3/F	Drowning	(b)(6) days post dose 2
QIV-007	TIV-YB	70/M	Hepatic cirrhosis	(b)(6)
QIV-007	TIV-YB	87/F	Hip Fracture	(b)(6)
QIV-006	Havrix	3/M	Drowning	(b)(6)days post dose 1

M=male; F=female; Q-QIV= FluLaval QIV; TIV-YB = TIV inactivated influenza vaccine containing the B/Yamagata influenza strain.

Source: Adapted from sBLA 125163/ SN 253, Module 2.7.4, Table 21, page 62

As expected, the majority of deaths occurred in adults; the causes of death were conditions commonly observed in the adult population. None of the six deaths in subjects who received FluLaval QIV were attributed by the investigator to the vaccine. The two pediatric deaths occurred in subjects who accidentally drowned. One of these deaths occurred within (b)(6) days of vaccination due to accidental drowning (Havrix arm) and was considered unrelated to study vaccine by the study investigator.

*Reviewer Comment: Overall, the studies submitted to the supplement did not demonstrate an increased risk of death associated with FluLaval QIV. The case narratives for all deaths were reviewed. In the opinion of this review, the investigator’s assessment regarding relatedness of deaths to study vaccine appeared reasonable.*

#### **8.4.2 Nonfatal Serious Adverse Events**

Two percent (117/5201) of subjects enrolled and vaccinated in the four clinical studies reported at least one non-fatal SAE during the entire study period. The nonfatal SAEs observed for both children and adults represented common diagnoses observed in the general population in the geographic locations where the study was conducted.

Among adults, 38 subjects reported non-fatal SAEs during the entire study period. Twelve nonfatal SAEs occurred within 30 days post-vaccination in subjects who received FluLaval QIV. None were considered vaccine-related. There was no imbalance in the number of nonfatal SAEs by study group.

Among children, 109 subjects reported nonfatal SAEs. Six nonfatal SAEs occurred within 30 days post-vaccination in subjects who received FluLaval QIV. Of these, two nonfatal SAEs (febrile convulsions) were considered vaccine-related. One of the two cases of febrile convulsion occurred 18 days after the first dose of FluLaval QIV arm in a 30 month old male subject and resolved the same day. The other case of febrile convulsion occurred in the Havrix group.

*Reviewer Comment: Overall, the studies in the FluLaval QIV development program did not identify safety concerns. Although one case of febrile convulsion related to FluLaval QIV occurred in a 30 month old male, this SAE did not occur within the population for whom the vaccine will be indicated (persons 3 years of age and older). No cases of febrile convulsion associated with FluLaval QIV were observed in subjects 3 years of age and older.*

#### **8.4.3 Study Dropouts/Discontinuations**

Less than 1% of subjects enrolled in studies of FluLaval QIV discontinued the study due to an AE. In the pediatric studies, 4 subjects were discontinued. Two subjects died due to accidentally drowning considered unrelated to vaccination. Two subjects experienced febrile convulsions; one of the two subjects, a 30 month old male, received FluLaval QIV. Six adult subjects were discontinued due to death considered unrelated to study vaccine (4 received FluLaval Q-QIV group; 2 received a comparator vaccine).

*Reviewer Comment: The numbers of discontinuations due to AEs do not raise concern regarding the safety of FluLaval QIV.*

#### **8.4.4 Common Adverse Events**

In adults, the most common ( $\geq 10\%$ ) solicited local adverse reaction was pain (60%); the most common solicited systemic AEs were muscle aches (26%), headache (22%), fatigue (22%), and arthralgia (15%). The unsolicited AEs that occurred most frequently ( $\geq 1\%$  of subjects) were nasopharyngitis, upper respiratory infection, headache, cough and oropharyngeal pain.

In children 3 through 17 years of age, the most common ( $\geq 10\%$ ) solicited local adverse reaction was pain (65%). In children 3 through 4 years of age, the most common ( $\geq 10\%$ ) solicited systemic AEs were irritability (26%), drowsiness (21%), and loss of appetite (17%). In children 5 through 17 years of age, the most common ( $\geq 10\%$ ) solicited systemic AEs were muscle aches (29%), fatigue (22%), headache (22%), arthralgia (13%), and gastrointestinal symptoms (10%). Unsolicited AEs that occurred most frequently ( $\geq 1\%$  of subjects FluLaval QIV) were vomiting, pyrexia, bronchitis, nasopharyngitis, pharyngitis, upper respiratory tract infection, headache, cough, oropharyngeal pain, and rhinorrhea,

#### **8.4.5 Clinical Test Results**

There were no clinical safety laboratory tests performed in any of the studies submitted to this supplement.

#### **8.4.6 Systemic Adverse Events**

In adults, the most common solicited systemic AEs were muscle aches (26%), headache (22%), fatigue (22%), and arthralgia (15%).

In children 3 through 4 years of age, the most common ( $\geq 10\%$ ) solicited systemic AEs were irritability (26%), drowsiness (21%), and loss of appetite (17%). In children 5 through 17 years of age, the most common ( $\geq 10\%$ ) solicited systemic AEs were muscle aches (29%), fatigue (22%), headache (22%), arthralgia (13%), and gastrointestinal symptoms (10%).

#### **8.4.7 Local Reactogenicity**

The clinical studies in the FluLaval development program demonstrated that, similar to other inactivated influenza vaccines, FluLaval QIV induced mild injection site pain in both children and adults.

Adults, not unexpectedly, frequently report injection site pain within 7 days post-vaccination with FluLaval QIV as shown in the following table.

**Table 50. Studies FLU Q-QIV-007 and FLU Q-QIV-(T+)-009: Percentages of Subjects  $\geq 18$  years of Age Reporting Solicited Local Adverse Reactions During 7 Days Post-Vaccination With FluLaval QIV**

Symptoms	FLU Q-QIV-007 (%)	FLU Q-QIV-(T+)-009 (%)
Pain	60	73
Grade 3	2	0
Redness	2	2
Grade 3	0	0
Swelling	2.5	2
Grade 3	0	0

Source: Adapted from sBLA 125163/ SN 253, Module 2.7.4, Tables 8 and 16; pages 30 and 49



Although the majority (60-73%) of adults subjects reported injection site pain following administration of FluLaval QIV, less than 2% of subjects experienced grade 3 injection site pain. Few (less than 3%) adults reported redness and swelling. Grade 3 erythema and swelling were not reported in the two clinical studies in adults.

A slightly higher percentage of adults reported injection site pain with FluLaval QIV compared to comparator vaccines TIV-VB (45%) and TIV-YB (41%).

*Reviewer Comment: Higher local reactogenicity associated with FluLaval QIV in adults is likely due to higher antigen content.*

A similar percentage of children 3 years of age and older reported injection site pain associated with FluLaval QIV as shown in the following table.

**Table 51. Studies FLU Q-QIV-003 and FLU Q-QIV-006: Solicited Local Adverse Reactions During 7 Days Post-Vaccination With FluLaval QIV in Children 3 years of Age and Older**

Symptoms	Type	FLU Q-QIV-003 <sup>a</sup> (%)	FLU Q-QIV-006 (%)
Pain	All	70	48
Grade 3 Pain	Grade 3	4	1.4
Redness	All	6.2	0.7
Grade 3 Redness	Grade 3	0.1	0
Swelling	All	7	1.8
Grade 3 Swelling	Grade 3	0.1	0

<sup>a</sup>Solicited local adverse reactions for subjects 6 through 35 months of age not included.

Source: Adapted from sBLA 125163/ SN 253, Module 2.7.4, Tables 10 and 13; pages 34 and 42.

Forty-eight to seventy percent of children reported injection site pain following FluLaval QIV. Grade 3 pain was uncommon (<1%). Erythema and swelling were reported in <1% of FluLaval recipients.

A higher percentage of children reported injection site pain with FluLaval QIV compared to Havrix (35%) and TIV-VB (59%) and TIV-YB (59%).

*Reviewer Comment: Higher local reactogenicity associated with FluLaval QIV in children is likely due to higher antigen content. The reactogenicity observed with FluLaval QIV is consistent with that of other inactivated influenza vaccines, including QIV vaccine, licensed to date. Reactogenicity associated with FluLaval was generally mild and largely secondary to injection site pain in both children and adults.*

## **8.5 Additional Safety Evaluations**

### **8.5.1 Dose Dependency for Adverse Events**

The same dose of FluLaval QIV was studied in adults and in children in the studies included in this supplemental BLA; therefore, there are no safety data to compare different antigen doses of the vaccine formulation. Of interest, the QIV formulation did have a higher antigen content than the control vaccine, however, safety results were similar for the QIV and TIV formulations. In addition, 3019 unprimed pediatric subjects 3 through 8 years of age received two study vaccinations administered 28 days apart. These subjects reported fewer adverse reactions after the second dose (39%) compared to the first dose of vaccine (46%) when administered 28 days apart.

### **8.5.2 Time Dependency for Adverse Events**

The majority of AEs post-vaccination occurred within one week post-vaccination. The majority of these AEs were mild and resolved by day 7. No other AEs had a consistent temporal relationship to study vaccination.

### **8.6 Safety Conclusions**

The clinical data submitted in this supplement support the safety of FluLaval QIV in persons 3 years of age and older. The results demonstrated that mild injection site pain may occur more frequently with FluLaval QIV than with the TIVs. Systemic AEs such muscle aches, headaches, fatigue and arthralgia, may occur in  $\geq 10\%$  of adults and older children (5 through 17 years of age). Young children 3 through 4 years of age may experience irritability, drowsiness and loss of appetite. No evidence for an increased risk of death, nonfatal SAEs, MAEs, or pIMDs was shown to be associated with FluLaval QIV.

## **9. ADDITIONAL CLINICAL ISSUES**

### **9.1 Special Populations**

#### **9.1.1 Human Reproduction and Pregnancy Data**

The safety of FluLaval in pregnant women was not studied. Pregnancy was an exclusion criterion for all female subjects of childbearing potential in the studies included in the FluLaval QIV development program. Across all the studies, there were a total of 8 pregnancies reported. Seven pregnancies led to delivery of live, healthy infants. One pregnancy resulted in a spontaneous abortion.

FluLaval QIV was assigned a pregnancy category B classification based on the results of a reproductive toxicity study and a female fertility and embryo-natal survival study which did not demonstrate significant toxic effects on female fertility.

Please see the review by Steven Kunder, Pharmacologist, Division of Vaccines and Related Products Applications, Office of Vaccine Research and Review, for details. Please refer to Section 4.6 for a description of the pharmacovigilance plan with respect to plans for the development of a pregnancy registry for this product.

#### **9.1.2 Use During Lactation**

FluLaval QIV has not been evaluated in nursing mothers. Whether the vaccine is excreted in human milk is unknown.

### 9.1.3 Pediatric Use and PREA Considerations

For children 3 through 17 years of age, PREA requirements were fulfilled by the submission of safety and immunogenicity and efficacy data from Studies QIV-006 and QIV-003.

The PREA requirement for studies in children 6 months through 35 months was deferred, because a non-inferiority, immunogenicity and safety study comparing FluLaval QIV to a US licensed QIV influenza vaccine in children 6 through 35 months of age is planned.

The PREA requirement for studies in infants under 6 months were waived because use of FluLaval QIV in infants under 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 Populations

FluLaval QIV has not been studied in immunocompromised populations.

### 9.1.5 Geriatric Use

Overall the safety and immunogenicity data generated in elderly subjects enrolled in studies FLU Q-QIV-007 and FLU Q-QIV-(T+)-009 supported the results of the clinical efficacy study in children (study FLU Q-QIV-006).

The vaccine was shown to be immunogenic in the elderly based on the percentage of subjects demonstrating seroconversion the percentage of subjects achieving an HI titer  $\geq 1:40$  (demonstrated by  $\geq 60\%$  subjects) for all influenza strains except for B/Victoria. The lower bound of the 95% CI for seroconversion rate to B/Victoria was slightly lower than 30%.

*Reviewer Comment: Roughly 70% of subjects enrolled in the adult study FLU Q-QIV 007 had received an influenza vaccine during at least one of the three prior seasons. High pre-vaccination HI titer to B/Victoria due to high rates of prior immunization or prior exposure to influenza viruses may explain the lower seroconversion rate to this particular strain. Of note, there is no known immune correlate that corresponds to protection from influenza infection.*

The safety data supported the use of FluLaval QIV in geriatric adults. The overall incidence of solicited and unsolicited AEs, including report of injection site pain, during the first four days of the study was lower in older adults (48%) compared to younger adults (82%). The most commonly observed solicited systemic adverse reactions were muscle pain in the older cohort. Grade 3 solicited local adverse reactions and systemic adverse reactions were rare. No differences in the percentage or type of unsolicited AEs, or SAEs reported were found between older and younger age groups.

*Reviewer Comment: The data did not raise concerns regarding the safety of FluLaval QIV in geriatric adults.*

### 9.1.6 Conclusions

- Data submitted to this supplement support the safety and efficacy of FluLaval QIV in geriatric adults 65 years of age and older.
- Insufficient data currently exist pertaining to the safety and effectiveness of FluLaval QIV in special populations such as immunocompromised persons.
- Insufficient data regarding the use of FluLaval QIV in children under 3 years of age exist, though the Applicant plans to study this age group as a postmarketing requirement (PMR).

## 10. CONCLUSIONS

- The clinical data submitted in this supplement support the traditional approval of FluLaval QIV for active immunization against influenza disease caused by the influenza A subtypes and type B viruses contained in the vaccine, in persons 3 years of age and older.
- In a large, randomized, observer-blind, non-influenza vaccine controlled study, FluLaval QIV demonstrated 55.4% efficacy (LL of 95% CI 39%) in the prevention of reverse-transcriptase polymerase chain reaction (RT-PCR)-confirmed influenza A and/or B disease presenting as ILI caused by community acquired influenza strains.
- The effectiveness of FluLaval QIV in children 8 through 17 years and in adults 18 years of age and older was demonstrated in two double-blind, randomized, controlled safety and immunogenicity studies. In both studies, control groups received one of two formulations of TIV, each containing one of the two lineage B viruses. Based on pre-specified success criteria, antibody responses to FluLaval QIV were non-inferior to TIV antibody responses for influenza A subtypes and corresponding B lineages, and superior to the opposite B lineage (e.g. B\Yamagata in Q-QIV vs. B\Victoria in TIV-VB).
- No safety concerns associated with FluLaval QIV were identified. Although FluLaval QIV causes increased injection site pain in children and adults (compared to TIVs), these reactions were mild, demonstrating that the addition of a second type B virus antigen to the QIV formulation does not lead to

substantially increased reactogenicity. No imbalances in the frequency or severity of solicited or unsolicited AEs or group of AEs were observed among the treatment arms within each study, and no increase in serious or uncommon conditions were observed in any group.

## **11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS**

### **11.1 Risk-Benefit Considerations**

A comparison of risks and benefits of licensure of FluLaval QIV for use in persons 3 years of age and older is presented in the following table and discussed in Section 11.2.

**Table 52. Risk-Benefit Considerations for Licensure of FluLaval Quadrivalent**

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> <li>• Influenza virus 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 U.S. annually.</li> <li>• Morbidity/mortality highest among the very young, the elderly, and those with underlying medical conditions.</li> <li>• Roughly 10% of hospitalizations result in death, mostly in elderly.</li> <li>• Since the late 1980s, two antigenically distinct B virus lineages have circulated, sometimes concurrently.</li> <li>• Influenza can cause pandemics.</li> </ul>	<ul style="list-style-type: none"> <li>• Influenza is a major cause of morbidity/mortality in the U.S.</li> <li>• A substantial proportion of infections result in serious or life-threatening disease, particularly among high-risk groups.</li> <li>• Illnesses caused by influenza B viruses represent a considerable proportion of overall influenza disease burden.</li> </ul>



Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Unmet Medical Need	<ul style="list-style-type: none"> <li>• The neuraminidase inhibitor class of antiviral drugs 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.</li> <li>• Resistance to one class of antivirals is now widespread, and strains resistant to oseltamivir have circulated widely in the past.</li> <li>• TIV 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 QIV vaccine, depending on B virus incidence, vaccine effectiveness, and vaccine supply for the specific season.</li> </ul>	<ul style="list-style-type: none"> <li>• Antivirals are effective for influenza prevention, but are operationally difficult to use, and resistance is a frequent concern.</li> <li>• Influenza vaccines are the most effective way of preventing morbidity and mortality due to influenza.</li> <li>• Inclusion of both B lineages as part of a QIV vaccine is projected to provide additional benefit in most seasons.</li> </ul>

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Clinical Benefit	<ul style="list-style-type: none"> <li>• Vaccine Efficacy</li> <li>• Additional protection for the alternate B lineage over that provided by the TIV vaccine is unknown.</li> <li>• Potential interference with the immunogenicity of the H1N1, H3N2 and B strain in the TIV by the second B strain.</li> </ul>	<ul style="list-style-type: none"> <li>• Vaccine efficacy (prevention of RT-PCR positive ILI) was demonstrated in a randomized, observer-blind, controlled clinical endpoint study in children 3 through 8 years of age.</li> <li>• Immunogenicity data in children (<math>\geq 3</math> years of age) and adults demonstrated that FluLaval QIV induced noninferior HI antibody responses against strains contained in a TIV.</li> <li>• Immunogenicity data demonstrated that FluLaval QIV induced higher HI antibody responses to the alternate B lineage than that induced by a TIV.</li> </ul>
Risk	<ul style="list-style-type: none"> <li>• Influenza vaccines have an extensive record of safety. FluLaval TIV has been licensed since in the U.S. 2006 and no safety signals in the U.S. have been identified through postmarketing surveillance to date.</li> </ul>	<ul style="list-style-type: none"> <li>• A total of 5,201 subjects (3,817 children and 1,384 individuals) comprise the safety database for FluLaval QIV.</li> <li>• The most substantial risks of vaccination with FluLaval QIV identified were associated with local adverse reactions at the injection site.</li> <li>• SAEs were uncommon.</li> </ul>

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	<ul style="list-style-type: none"><li data-bbox="431 260 959 436">• The most common adverse reactions following vaccination with FluLaval QIV, including local injection site reactions and systemic reactogenicity, are mild and self-limited.</li><li data-bbox="431 478 959 695">• 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.</li></ul>	<ul style="list-style-type: none"><li data-bbox="1000 260 1414 436">• The risks observed in the trials submitted in support of FluLaval QIV approval will be summarized in the package insert.</li><li data-bbox="1000 478 1398 695">• The Applicant agreed to establish a pregnancy registry of a prospective cohort study with active recruitment of exposed and unexposed women.</li></ul>

## 11.2 Risk-Benefit Summary and Assessment

Data submitted to this supplement supported the clinical efficacy of FluLaval QIV against RT-PCR positive ILI in children 3 through 8 years of age. Immunogenicity in children ( $\geq 3$  years of age), adults ( $\geq 18$  years of age) was demonstrated by non-inferior HI antibody responses compared to the strains in TIV common to both vaccines and higher HI antibody responses for the alternate B lineage over that provided by the TIV vaccine.

The most common risk associated with FluLaval QIV for both children and adults is pain at the injection site (60-65%); muscle aches, headaches, fatigue and arthralgia also occur in adults. Younger children (3 through 4 years of age) may experience drowsiness, loss of appetite and irritability following vaccination with FluLaval QIV. Overall, these AEs are mild.

It is the clinical reviewers' assessment that the minimal risks associated with FluLaval Quadrivalent vaccine, considered with the demonstrated efficacy in preventing influenza disease in children, and the added protection expected in children and adults from broader coverage of influenza B strains, results in a favorable overall risk-benefit determination.

## 11.3 Recommendations on Regulatory Actions

In the opinion of the reviewers, the safety and immunogenicity and efficacy data provided in this supplement support the traditional approval of FluLaval QIV for active immunization of persons 3 years of age and older against the influenza subtypes A and type B viruses contained in the vaccine.

## 11.4 Labeling Review and Recommendations

Revisions to the package insert and carton and container labels were negotiated with the Applicant. The issues discussed included the characterization of results pertaining to the secondary endpoint for study FLU Q-QIV-006, vaccine efficacy for the prevention of "moderate to severe influenza." Although CBER acknowledged the value of attempting to define a clinically meaningful endpoint that better describes prevention of influenza characterized by symptoms and outcomes more severe than mild upper respiratory complaints, CBER did not agree with the definition of 'moderate to severe influenza' proposed by the Applicant. The (non-validated) definition of moderate to severe influenza proposed by the Applicant included an aggregate of thirteen different illnesses or symptoms (fever ( $> 39^{\circ}\text{C}$ ) alone, or shortness of breath, pulmonary congestion, pneumonia, croup, wheezing, acute otitis media, encephalitis, myositis, seizure, myocarditis, bronchiolitis, or bronchitis). The results indicated that ILI with high fever ( $> 39^{\circ}\text{C}$ ) was the most frequent manifestation of 'moderate to severe influenza.' The data pertaining to this secondary objective were displayed in the package insert as an incidence rate for each separate outcome, not as a composite.

A second labeling issue discussed was the description, in the package insert, of the result of an exploratory analysis of vaccine efficacy against RT-PCR positive ILI in subjects 3 through 4 years of age, relative to children 5 through 8 years of age (study FLU Q-QIV-006). The result suggested reduced vaccine efficacy in children 3 through 4 years of age. As the study was not designed to answer this question, the clinical significance of this finding is unknown. This result of the exploratory subgroup analysis was included in the package insert.

### **11.5 Recommendations on Postmarketing Actions**

As a postmarketing commitment, the Applicant agreed to establish a pregnancy registry to prospectively enroll women exposed to FluLaval QIV during pregnancy and collect data on their outcomes and newborn health status. The protocol submission date is October 31, 2013.

As a postmarketing requirement, the Applicant agreed to conduct a study to assess the non-inferior immunogenicity of FluLaval QIV to a licensed influenza vaccine in children 6 through 35 months of age. The protocol submission data is June 30, 2014.

