BLA Clinical Review Memorandum

Application Type	Supplemental Biologics License Application
STN	125127\834
CBER Received Date	15 March 2017
PDUFA Goal Date	12 January 2018
Division / Office	Division of Vaccines and Related Product Applications/ Office of Vaccine Research and Review
Priority Review (Yes/No)	No
Reviewer Name	Susan K. Wollersheim, MD
Review Completion Date / Stamped Date	
Supervisory Concurrence	Lucia Lee, MD, Team Leader
	Jeff Roberts, MD, Branch Chief
Applicant	GlaxoSmithKline Biologicals, Inc.
Established Name	Influenza Virus Vaccine
(Proposed) Trade Name	Fluarix Quadrivalent®
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	**Antigens** Each 0.5mL dose contains 15µg HA each (60µg total) of the four influenza strains recommended annually including: A/H1N1 A/H3N2 B/Yamagata B/Victoria **Excipients** Polysorbate 80 (Tween 80), octoxynol 10 (Triton X-100), alphatocopheryl hydrogen succinate, sodium chloride, (b) (4) and water for injection.
Dosage Form(s) and Route(s) of Administration	Suspension for intramuscular injection .
Dosing Regimen	-Ages 6 months through 8 years not previously vaccinated with influenza vaccine: two 0.5 mL doses at least 4 weeks apart. -Ages 6 months through 8 years vaccinated with influenza vaccine in a previous season: one or

	two 0.5 mL doses each, depending on ACIP recommendations. -Ages ≥ 9 years: one 0.5mL dose.
Indication(s) and Intended Population(s)	Fluarix Quadrivalent is a vaccine indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. Fluarix is approved for use in persons 3 years of age and older. The purpose of this efficacy supplement is extend the use of Fluarix Quadrivalent to 6 months of age. The indication is unchanged.
Orphan Designated (Yes/No)	No

TABLE OF CONTENTS

GLOSSARY

AE	Adverse Event
AR	Adverse Reaction
AOM	Acute otitis media
ATP	According to protocol
BIMO	Bioresearch monitoring
CI	Confidence interval
FDA	Food and Drug Administration
FLU D-QIV	Fluarix Quadrivalent Influenza Vaccine
GMT	Geometric mean titers
GSK	GlaxoSmithKline
HA	Hemagglutinin antigen
HI	Hemagglutinin inhibition
ICU	Intensive care unit
ILI	Influenza like illness
IM	Intramuscular
ITP	Immune thrombocytopenia purpura
LL	Lower limit
LRI	Lower respiratory tract infection
MAE	Medically attended adverse events
MAV	Medically attended visits
(b) (4)	
PI	Package insert
pIMD	Potential Immune-Mediated Disease
PMR	Post Marketing Requirement
PREA	Pediatric Research Equity Act
QIV	Quadrivalent influenza vaccine
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard Deviation
SCR	Seroconversion rate
sBLA	Supplemental Biologics Licensing Application
TIV	Trivalent influenza vaccine
TVC	Total Vaccinated Cohort
UL	Upper limit
URI	Upper respiratory tract infection
VE	Vaccine Efficacy

1. Executive Summary

This supplemental Biologics License Application (sBLA) was submitted by GlaxoSmithKline Biologicals (GSK) to support use of Fluarix Quadrivalent (FLU D-QIV) in individuals 6 months to 3 years of age. FLU D-QIV is a seasonal quadrivalent split-virion, inactivated influenza virus vaccine containing a total dose of 60 µg (15 µg per strain) of hemagglutinin antigen (HA) prepared from virus propagated in the allantoic cavity of embryonated hens' eggs. The product is currently approved for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine in persons ages 3 years and older.

The sBLA includes efficacy, immunogenicity, and safety data from a single phase 3 clinical trial (Study FLU D-QIV 004) conducted in children ages 6 through 35 months. Study FLU D-QIV 004 was a randomized, observer blind, multi-center, controlled trial that compared the efficacy, immunogenicity, and safety of FLU D-QIV to non-influenza vaccine controls in subjects 6 through 35 months of age. Of the 12,018 subjects enrolled, 6006 received FLU D-QIV and 6012 received a non-influenza vaccine control (*Prevnar13, Havrix, and/or Varilrix/Varivax/ProVarivax*, depending on age). Vaccine-primed subjects received a single IM dose of study vaccine whereas vaccine-unprimed subjects received 2 doses 28 days apart. All subjects <12 months of age were considered vaccine unprimed. For the efficacy assessment, all subjects were followed through active and passive surveillance for influenza like illness (ILI; defined as a temperature ≥ 38.0°C and at least one of the following symptoms: cough, runny nose, nasal congestion or breathing difficulty) to obtain a nasal swab specimen for influenza testing. For the immunogenicity assessment, a subset of subjects had blood samples taken on Day 0 and 28 days after completion of the vaccine series (Day 28 for vaccine-primed subjects and Day 56 for vaccine-unprimed subjects) for immune response testing.

The primary efficacy objectives were prevention of reverse transcriptase polymerase chain reaction (RT-PCR) confirmed influenza A and/or B disease (with adverse outcomes associated with influenza infection or of any severity) due to any seasonal influenza strain, when compared to non-influenza controls. The pre-specified criteria for efficacy of FLU D-QIV as compared to the non-influenza vaccine controls were met for both primary objectives. In addition, a secondary objective demonstrated that FLU D-QIV was efficacious in the prevention of culture confirmed influenza A and/or B of any severity due to antigenically-matching influenza strains contained in the vaccine.

The safety evaluation in Study FLU D-QIV-004 included collection of local and systemic solicited adverse events (AEs) captured via diary card for 7 days post vaccination; unsolicited adverse events, serious adverse events (SAEs), potentially immune mediated diseases (pIMDs), medically attended visits (MAVs), and deaths were collected for the study duration (6-8 months). Except for pIMDs, the frequency of adverse events were similar between the FLU D-QIV and control groups. Five subjects in the FLU D-QIV group experienced at least one pIMD and three of them were considered possibly related to the vaccine (nephrotic syndrome, Idiopathic thrombocytopenic purpura, and Bell's Palsy). There were no pIMDs in the control group. The pattern of diagnoses and temporal relationship to vaccination did not suggest a causal relationship between vaccination and pIMD. In addition, these conditions can occur within the general pediatric population and the number of subjects affected in this study were within the background rate of each event among the general pediatric population. The nature and severity of unsolicited AEs, MAVs, and SAEs were similar between treatment groups. There were four deaths reported (one in the FLU D-QIV group) and none of the deaths were considered attributable to the study vaccine.

The applicant fulfilled the Pediatric Research Equity Act (PREA) postmarketing requirement to evaluate Fluarix Quadrivalent in children ages 6 through 35 months as specified in the 14 December 2012 approval letter for STN #125127/513. Because the manufacturing process is the same for the trivalent formulation of Fluarix, except that it does not contain one of the two influenza B strains contained in the quadrivalent

formulation, the conclusions of this supplement, including fulfillment of the PREA requirement, can be applied to both products.

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

The data submitted by the applicant in this sBLA support approval of Fluarix and Fluarix Quadrivalent for active immunization of children ages 6 months through 35 months against influenza disease caused by influenza subtypes A and type B contained in the vaccine.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The study was not powered to detect differences in efficacy, immunogenicity or safety with regard to gender or geographical ancestry. Post-hoc analyses suggested efficacy, immunogenicity and safety to be comparable across genders and across geographic ancestry (White/Caucasian, Asian, Others).

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Influenza is an acute, highly contagious, respiratory disease condition caused by influenza viruses, mainly spread through respiratory droplets. The illness is accompanied by fever and variable degrees of other systemic symptoms, ranging from mild fatigue to respiratory failure and even death. Influenza occurs in annual epidemics that are associated with significant morbidity and mortality and have substantial public health impact. Annual influenza epidemics are responsible for an estimated 3 to 5 million cases of severe illness and a quarter to half a million excess deaths worldwide annually (1). The highest risk of complications occur among children aged 6-59 months, adults aged 65 years or older, pregnant women, and people of any age with underlying chronic conditions that put them at risk for influenza disease (1).

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

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

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

Currently, there are four FDA-licensed antiviral drugs are available for use in the United States (Tamiflu®, Relenza®, Symmetrel® and Flumadine®). Of these, only the neuraminidase inhibitors, Tamiflu and Relenza, are currently recommended for use by the Centers for Disease Control and Prevention. Use of adamantine class derivatives (Symmetrel and Flumadine) is no longer recommended because many strains of influenza, including the 2009 H1N1 influenza, are now resistant to this class of drugs. Although neuraminidase inhibitors are currently effective against most seasonal influenza viruses, resistance to drugs in this class has developed sporadically (9), with most of the benefit derived when given prophylactically or early in the disease course. However, none of these drugs are indicated for the prevention of influenza.

2.3 Safety and Efficacy of Pharmacologically Related Products

Inactivated whole-virus influenza vaccines have been commercially available since the 1940s. Currently, eight inactivated split-virus influenza vaccines are licensed in the U.S. Of these, only four (Fluzone, Fluzone Quadrivalent, FluLaval and FluLaval Quadrivalent) are approved for children 6 through 35 months of age. A recent meta-analysis of 31 studies conducted between 1967 and 2011 calculated a pooled efficacy of 59% in healthy adults against laboratory-confirmed influenza illness (10). Data regarding the efficacy of vaccination against influenza-related hospitalization and other severe outcomes also indicate that some protection is conferred (11).

The most frequent adverse events after seasonal inactivated influenza vaccination are local adverse reactions, resulting in pain, erythema and induration in up to 65% of individuals. Serious adverse events associated with influenza vaccination are uncommon. Anaphylaxis has been reported after influenza vaccination, but occurs rarely (0-10 per million doses of vaccine (11). Increased rates of Guillain-Barré syndrome (GBS) were reported during the swine influenza virus vaccination campaign of 1976. Observational studies since then have identified an increased risk of at most 1 additional GBS case per million vaccinated persons associated with seasonal influenza vaccines. Influenza vaccination has also been associated in passive surveillance studies with an increased rate of febrile seizures in children, potentially related to co-administration with pneumococcal conjugate vaccine (Prevnar13)(12).

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

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

Fluarix (Trivalent) was approved by the FDA in August 2005. Fluarix Quadrivalent was approved for immunization of adults and children 3 years of age and older by the US FDA in December 2012 and has since been approved in the United Kingdom, France and Germany Austria, Belgium, Czech Republic, Italy, Slovak Republic, Spain, Switzerland, Australia and Turkey. Based on distribution data it is estimated that over (b) (4) million doses have been administered. Routine pharmacovigilance monitoring of these products has not identified any safety signals.

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

Fluarix (Trivalent) was approved under accelerated approval on 31 August 2005 in the United States for the prevention of influenza in adults 18 years of age and older. Because products approved under the accelerated approval require further studies that are adequate and well controlled to verify and describe clinical benefit, a clinical endpoint efficacy study was conducted in adults 18 through 49 years of age. The efficacy of Fluarix was confirmed in this clinical endpoint study and Fluarix was granted 'traditional approval' on 2 October 2009. Expansion of the age indication for children aged 3 years and older was approved on 19 October 2009 (STN 125127/319) Fluarix Quadrivalent (FLU D-QIV) was approved on 14 December 2012 in the United States for the prevention of influenza (STN 125127/513) in persons 3 years and older. This study was conducted to fulfill the PREA Post Marketing Requirement (PMR) from the initial approval of FLU D-QIV.

In March 2011, a special protocol assessment of the FLU D-QIV 004 protocol was requested and written responses were provided by CBER in April 2011.

- The proposed primary endpoints were prevention of RT-PCR confirmed influenza A and/or B due to any seasonal influenza strain and culture-confirmed influenza due to vaccine matching and any influenza strains, and manifestations of influenza such as moderate to severe influenza, acute otitis media and lower respiratory illnesses. We agreed with study design, but expressed concerns about the use of moderate to severe influenza (defined as a subset of influenza disease with any of the following: fever >102.2°F, physician-diagnosed acute otitis media, physician-diagnosed lower respiratory tract illness, physician-diagnosed serious extra-pulmonary complications, hospitalization in the intensive care unit, or supplemental oxygen required for more than 8 hours) as a primary endpoint because their definition included an aggregate of medical conditions that differ widely in severity (fever vs. encephalitis), there is no validated case definition for AOM or LRI, and it is not a widely accepted standard clinical endpoint in vaccine trials. We expressed the same concerns at a Type A meeting held in June 2011, in written correspondence in August 2012 and at teleconference held in December 2012.
- Regarding secondary efficacy endpoints that include acute otitis media (AOM) and lower respiratory infection (LRI), CBER agreed that the use of these clinical entities to trigger nasal swab collection would be helpful, but not the use of them as endpoints given the difficulty in consistent diagnosis of each.

In June 2011, a Type A meeting was held to further discuss the FLU D-QIV 004 protocol. We again emphasized our concern about the usefulness of moderate to severe disease as a study endpoint. More narrow and reproducible definitions of severe influenza were suggested. We again stated our preference for vaccine efficacy against vaccine matching culture confirmed influenza as an important endpoint. The applicant declined to change the endpoint because the use of PCR rather than culture resulted in a higher attack rate and that there was no reliable way to infer antigen matching based on sequencing in a timely manner for assessing the attack rate and accrual of confirmed influenza cases for the analyses.

In August 2012, due to the availability of data from a related influenza vaccine manufactured by the same applicant that indicated that the vaccine efficacy assumption was too high, and thus the power calculation used for study FLU D-QIV 004 was no longer appropriate (study FLU Q-QIV-006; see clinical review for STN 125163/253; https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM483150.pdf), the primary endpoints were revised by the applicant, as follows: (a) to the prevention of RT-PCR confirmed moderate to severe influenza due to any influenza strain and (b) RT-PCR confirmed influenza of any severity due to any influenza.

In December 2012, a teleconference was held to further discuss these primary endpoint revisions. We re-stated our recommendation against including moderate to severe influenza disease as a primary endpoint and the definition of serious influenza disease was revised according to our recommendations

In January and March 2013, additional protocol amendments were submitted in response to CBER comments. The applicant acknowledged that prevention of culture confirmed influenza due to influenza strains contained in the vaccine provides the most easily interpretable estimate of vaccine efficacy. But because the timing was infeasible to identify antigenically matched cases and make decisions on the need to accrue additional cases for the efficacy analysis, they still planned to use RT-PCR confirmed influenza for the primary efficacy endpoints and analyze the prevention of vaccine matching culture confirmed influenza as a secondary objective.

In August 2013, the applicant was granted a deferral extension request to December 2015, to allow enrollment of additional subjects.

In November 2015, the applicant was granted a second deferral extension request to January 2017, to allow additional time for assay validation and analysis of results.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized to accommodate the conduct of a complete clinical review without difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Bioresearch monitoring (BIMO) inspections were conducted for four international clinical sites supervised by two different clinical investigators for the pivotal study submitted to this sBLA, FLU D-QIV-004. The data review at the inspected study sites represented approximately 15.5% percent of enrolled subjects the pivotal study. The inspections revealed no issues that would impact the data submitted in this BLA. For full details please refer to the BIMO review memo dated 6 December 2017.

3.3 Financial Disclosures

Financial disclosures for the studies evaluated in this sBLA are listed below in Tables 1-3.

Table 1. Financial Disclosures for Study FLU-D-QIV-004

Covered clinical study (name and/or number): **FLU-D-QIV-004**		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 98		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1* Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		

*One sub-investigator for FLU-D-QIV-004 received (b) (4), (b) (6) in educational grants and recruited 44 subjects from one site and 8 subjects from another. As these subjects represented a small percentage of the total recruitment (n=12,045), it was thought unlikely to affect outcome of the study.

Table 2. Financial Disclosures for Study FLU-D-QIV-009

Covered clinical study (name and/or number): **FLU-D-QIV-009**		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 27		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

Table 3. Financial Disclosures for Study FLU-D-QIV-015

Covered clinical study (name and/or number): **FLU-D-QIV-015**		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 53		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

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

4.1 Chemistry, Manufacturing, and Controls

A formal chemistry, manufacturing, and controls review was not conducted for this sBLA since this product is currently licensed and no formulation changes were made.

4.2 Assay Validation

The following assay validation reports were reviewed independently by chemistry, manufacturing and controls and statistical reviewers: RT-PCR followed by (b) (4) Hemagglutination inhibition (HI) assay for antigenic characterization of strains (H1N1, B subtypes), (b) (4) assay for antigenic characterization (H3N2), and the applicant's (b) (4) assays. The RT-PCR and (b) (4) assay were each found to be fit for the intended use and the HI assay appeared to perform adequately. The applicant's (b) (4) assays were adequate in detection of neutralizing antibody against vaccine viruses. For full details of the assay validation reviews, please refer to the review memo from the Division of Viral Products dated 27 November 2017 and the review memo from the Office of Biostatistics and Epidemiology dated 1 December 2017.

4.3 Nonclinical Pharmacology/Toxicology

A formal nonclinical pharmacology/toxicology review was not conducted for this sBLA as they were previously submitted and reviewed under the original BLA.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Vaccination against influenza results in an immune response that can be quantified by elevation in serum HI titers. Some studies and meta-analyses associate HI titers ≥ 1:40 with 50% reduction in the risk of contracting influenza, based on controlled, influenza challenge studies in adults. Antibody against one influenza virus type/subtype confers little or no protection against another virus. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type/subtype. Frequent development of antigenic variants through antigenic drift is the

virological basis for seasonal epidemics and the reason for the usual replacement of one or more influenza viruses in each year's influenza vaccine.

4.5 Statistical

Statistical review confirmed the vaccine efficacy of FLU D-QIV as compared to non-influenza controls. The reviewer noted that the subgroup analysis of vaccine efficacy in the 6 through 11 month old infants was lower than in the overall 6 through 35 month old children and this is discussed below in Section 6.1.11.3. The study was not powered to determine if the differences in age were statistically significant. In addition, this 6 through 11 month age subgroup had the lowest number of enrolled subjects, and this difference in vaccine efficacy was not found to be clinically relevant. For full details of the statistical review, please refer to the review memo from the Office of Biostatistics and Epidemiology dated 1 December 2017.

4.6 Pharmacovigilance

No changes were recommended to the routine pharmacovigilance plan proposed for FLU D-QIV. No postmarketing safety studies or risk evaluation and mitigation strategies were recommended. For full review of the Applicant's pharmacovigilance plan please refer to the review memo from the Office of Biostatistics and Epidemiology dated 22 December 2017.

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

5.1 Review Strategy

Reports for 3 studies were included in this sBLA:

- Study, FLU D-QIV-004: efficacy and safety data from this phase 3 study serve as the primary basis to support the applicant's request for extending the lower age range. See Section 6.1 for more details.
- Supportive study FLU D-QIV-009: an extension of Study FLU D-QIV-004. The main study objective was to assess Fluarix QIV revaccination in subjects who were vaccinated (in study FLU D-QIV 004) in the preceding influenza season.
- Supportive study FLU D-QIV-015: safety and immunogenicity data in older children and adults were previously reviewed (see clinical review for STN 125127/775) to support a change in the manufacturing process. An annex, which included the safety and immunogenicity data from children 6 through 35 months of age, to the report was submitted to this sBLA to support the manufacturing bridging of the FLU D-QIV-004 and FLU D-QIV-009 study data (generated with the process licensed at the time the study conduct) to the new FLU D-QIV manufacturing process. See section 6.2.

The data from the two supportive studies are evaluated in the integrated summary of safety, primarily for safety signals such as SAEs and deaths, and do not contribute to an integrated summary of efficacy because they were smaller descriptive studies that did not evaluate the same primary efficacy endpoints as Study FLU D-QIV-004 and they used different active comparators from Study FLU D-QIV-004, both of which were FLU D-QIV formulations.

The three studies are summarized below in Table 4.

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

The following files served as the basis for the clinical review of STN 125127/834:

STN 125127/834.0

- m1.3.4 Financial Disclosures
- m1.14 Labeling
- m2.5 Clinical Overview
- m2.7 Clinical Overview
- m5 Clinical Study Reports
- Amendments 1 through 10 were reviewed for materials relevant to the clinical review process.

5.3 Table of Studies/Clinical Trials

Table 4. Overview of Studies FLU-D-QIV-004, FLU-D-QIV-009, and FLU-D-QIV-015

Study number (NCT number) Year(s) **Total Subjects**	**Countries (number of sites)**	**Study Design**	**Population (age)** **Schedule of Vaccination**	**Study groups** **Administered Vaccine**	**Total number of subjects per group**
FLU-D-QIV-004 (NCT01439360) 2011-2014 N=12,018	Bangladesh Belgium Czech Republic Dominican Republic Honduras India Lebanon Philippines Poland Spain Thailand Turkey United Kingdom 106 sites	Phase 3 Efficacy study, observer blind, randomized 1:1, multi-center, non-influenza vaccine comparator controlled	Children (6 through 35 months) enrolled in 5 independent cohorts Subjects <12 months: 2 doses (Days 0, 28) Subjects ≥12 months and vaccine-primed (seasonal influenza): 1 dose (Day 0) Subjects ≥12 months and vaccine-unprimed (seasonal influenza): 2 doses (Days 0, 28)	**D-QIV group:** D-QIV (1 or 2 doses) **Control group:** -Subjects <12 months: *Prevnar13* -Subjects ≥12 months and vaccine primed: *Havrix* -Subjects ≥12 months and vaccine-unprimed: *Havrix* + varicella vaccine (*Varilrix or Varivax/ProVarivax*)	6006 6012

FLU-D-QIV-009 (NCT01702454) 2014-2015 N=470	Czech Republic Poland Spain United Kingdom	Phase 3 Revaccination study, open label, multi-center, active controlled extension of FLU-D-QIV-004, cohort 1	Children (17 to 48 months) from cohort 1 of study FLU D-QIV-004 who received 2 doses of D-QIV or 2 doses of non-influenza control vaccine **Vaccine-primed subjects:** 1 dose (Day 0) **Vaccine-unprimed subjects (control):** 2 doses (Days 0, 28)	**Vaccine-primed:** 1 dose D-QIV **Vaccine unprimed (control):** 2 doses D-QIV	241 229
FLU D-QIV-015 [a] (NCT02207413) 2014-2015 N=940	Bangladesh France Germany Spain Poland	Phase 3 New manufacturing process study, randomized 1:1, double-blind, multi-center	Children (6 through 35 months) Vaccine-primed subjects: 1 dose (Day 0) Vaccine-unprimed subjects: 2 doses (Days 0, 28)	**D-QIV-IP:** FLU D-QIV-IP (investigational vaccine, harmonized process) **D-QIV-LP:** FLU D-QIV-LP vaccine (licensed process)	466 474

Source: Adapted from STN 125127/834.0: module 2.5 Clinical Overview and module 2.7.6 Synopses of Individual Studies.
[a] Only the study design for the children 6 months through 35 month age group is summarized here.

5.4 Consultations

5.4.1 Advisory Committee Meeting

Multidisciplinary review of the data submitted for this supplement did not reveal new issues about the product that required the opinion of an independent panel of experts. including the Vaccines and Related Biological Products Advisory Committee.

5.5 Literature Reviewed

1. WHO Fact Sheet November 2016. At http://www.who.int/mediacentre/factsheets/fs211/en/

2. Schanzer D, Langley J, Tam T. Hospitalization Attributable to Influenza and Other Viral Respiratory Illnesses in Canadian Children. Pediatr Infect Dis J 2006;25:795-800.
3. CDC (Centers for Disease Control and Prevention). Influenza vaccination coverage among children aged 6-23 months--United States, 2005-06 influenza season. MMWR 2007;56(37):959-63.
4. Poehling KA, Edwards KM, Weinberg GA, Szilagyi P et al, for the New Vaccine Surveillance Network. The under-recognized burden of influenza in young children. NEJM 2006;355:31-40.
5. Brownstein JS, Mandl KD. Pediatric population size is associated with local timing and rate of influenza and other acute respiratory infections among adults. Ann Emerg Med 2008;52:63-8.
6. Barr IG, McCauley J, Cox N et al. Writing Committee of the World Health Organization Consultation on Northern Hemisphere Influenza Vaccine Composition for 2009–2010. Epidemiological, antigenic and genetic characteristics of seasonal influenza A (H1N1), A (H3N2) and B influenza viruses: Basis for the WHO recommendation on the composition of influenza vaccines for use in the 2009-2010 Northern Hemisphere season. Vaccine 2010;28(5) :1156-67. Online version of manuscript accessed for Table (Dec 2009).
7. Ambrose CS, Levin MJ. The rationale for quadrivalent influenza vaccines. Hum Vaccin Immunother. 2012;8(1):81–8.
8. Belshe RB, Coelingh K, Ambrose CS, et al. Efficacy of live attenuated influenza vaccine in children against influenza B viruses by lineage and antigenic similarity. Vaccine. 2010;28(9):2149–56.
9. Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, Cox NJ, Fukuda K. Influenza-associated hospitalizations in the United States. JAMA. Sep 15, 2004; 292(11):1333-40
10. 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.
11. Reed C, Meltzer MI, Finelli L, Fiore A. Public health impact of including two lineages of influenza B in a quadrivalent seasonal influenza vaccine. Vaccine. 2012 Mar 2;30(11):1993-8.
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. Hobson D, Curry RL, Beare AS, Ward- Gardner A. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. *J. Hyg. (Lond.)* 70(4): 767–777 (1972).
14. Reber A, Immunological assessment of influenza vaccines and immune correlates of protection. Expert Rev Vaccines 12 (5):519-36 (2013).
15. Ohmit SE, Petrie JG, Cross RT, Johnson E, Monto AS. Influenza hemagglutination inhibition antibody titer as a correlate of vaccine-induced protection*. J. Infect. Dis.* 204(12): 1879–85 (2011).
16. Febrile Seizures Fact Sheet. http://www.ninds.nih.gov/disorders/febrile_seizures/detail_febrile_seizures.htm

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study FLU-D-QIV-004

Title: A phase 3, observer-blind, randomized, multi-country, non-influenza vaccine comparator-controlled study to demonstrate the efficacy of GlaxoSmithKline Vaccines' quadrivalent seasonal influenza candidate vaccine GSK2321138A (Fluarix Quadrivalent; FLU D-QIV), administered intramuscularly in children 6 through 35 months of age.

The first subject was enrolled in the study on 1 October 2011 and the study was completed on 31 December 2014. The data lock point (date of database freeze) was on 13 July 2016.

6.1.1 Objectives

This study was designed to assess vaccine efficacy in children 6 through 35 months of age. The primary and secondary objectives are listed below.

Primary Objectives:

- To evaluate the efficacy of FLU D-QIV in the prevention of reverse transcription polymerase chain reaction (RT-PCR) confirmed moderate to severe influenza A and/or B disease due to any seasonal influenza strain, when compared to non-influenza vaccine controls in children aged 6 through 35 months.
- To evaluate the efficacy of FLU D-QIV in the prevention of RT-PCR confirmed influenza A and/or B disease of any severity due to any seasonal influenza strain, when compared to non-influenza vaccine controls in children aged 6 through 35 months.

Reviewer Comment: *The primary objective contains a composite endpoint designated as "moderate to severe influenza" which includes a wide range of adverse outcomes associated with influenza, ranging from fever >39 °C to hospitalization requiring supplemental oxygen. In addition, this composite endpoint is not a universally recognized standard definition of moderate to severe influenza and includes subjective diagnoses such as acute otitis media (AOM) and lower respiratory tract infection (LRI). Thus, this review uses the terminology "adverse outcomes associated with influenza infection" instead of "moderate to severe influenza."*

Secondary Objectives:

Efficacy:

To evaluate the efficacy of FLU D-QIV in the prevention of:

- Lower respiratory illness (LRI) associated with RT-PCR confirmed influenza A and/or B, when compared to non-influenza vaccine controls.
- Culture confirmed moderate to severe influenza A and/or B disease due to antigenically-matching influenza strains when compared to non-influenza vaccine controls.
- Culture confirmed influenza A and/or B disease of any severity due to antigenically-matching influenza strains when compared to non-influenza vaccine controls.
- Culture confirmed moderate to severe influenza A and/or B disease due to any seasonal influenza strain, when compared to non-influenza vaccine control.

- Culture confirmed influenza A and/or B disease of any severity due to any seasonal influenza strain, when compared to non-influenza vaccine controls.
- Acute otitis media (AOM) associated with RT-PCR confirmed influenza A and/or B, when compared to non-influenza vaccine controls.
- RT-PCR confirmed severe influenza A and/or B disease, when compared to non-influenza vaccine controls.

Immunogenicity:

- To evaluate the immunogenicity of FLU D-QIV in terms of hemagglutination inhibition (HI) antibody response 28 days after completion of vaccination, in an immunogenicity (immuno) subcohort of subjects.

Reactogenicity/safety:

- To evaluate the reactogenicity of FLU D-QIV and non-influenza vaccine controls in terms of solicited local and general adverse events (AEs) during 7 days after each vaccination and unsolicited symptoms during 28 days after each vaccination.
- To evaluate the safety of FLU D-QIV and non-influenza vaccine controls in terms of AEs with medically attended visits (MAVs), serious adverse events (SAEs) and potential Immune-Mediated- Diseases (pIMDs) during the entire study period (6 to 8 months after study start).

6.1.2 Design Overview

This study was a Phase 3, observer-blind, randomized, multi-country, multi-center, non-influenza vaccine comparator-controlled study with parallel treatment groups in children 6 through 35 months of age. Subjects were randomized 1:1 to receive either FLU-D-QIV or an age appropriate non-influenza control vaccine.

A total of 12,046 subjects were enrolled in 5 independent cohorts across 5 different influenza seasons (one cohort per season, 2011-2014) in different regions of the world (Asia, Europe, Central America). The study duration was approximately 6-8 months for each subject.

All subjects were followed with active and passive surveillance for influenza like illness (ILI), physician diagnosed lower respiratory infection (LRI), or physician diagnosed acute otitis media (AOM) to obtain a nasal swab specimen in a within 7 days of onset (ILI was defined as temperature ≥38ºC and at least one of the following symptoms: cough, runny nose, nasal congestion or difficulty breathing).

For immunogenicity assessments, two blood samples were collected: one on Day 0 (immune sub-cohort only) and the second on Day 28 after the last vaccination (Day 28 for vaccine-primed subjects and Day 56 for vaccine-unprimed subjects) for antibody testing.

Subjects were randomized at each study center by a central internet randomization program to receive either FLU D-QIV or non-influenza control.

Data was collected in an observer-blind manner. By observer-blind, it is meant that during the course of the study, the subject, subject‘s parent(s)/LAR(s), and those responsible for the evaluation of any study endpoint (e.g. safety, reactogenicity,

laboratory results) were all to be unaware of the treatment assignments. Therefore, vaccine preparation and administration were done by authorized medical personnel who were not to participate in any of the study clinical evaluations.

Subjects were followed for solicited AEs by diary card through Day 7 post vaccination. Unsolicited AEs were collected 28 days after the last vaccination (Day 28 for vaccine-primed and Day 56 for vaccine-unprimed subjects). Medically attended adverse events (MAEs), AEs leading to study withdrawal, potentially immune mediated diseases (pIMDs), and SAEs including deaths were monitored for 180 days following vaccination.

***Reviewer Comment**: The utilization of randomization at the center level was appropriate to minimize bias.See reviewer comment in Section 6.1.4 below for assessment of blinding procedures.*

6.1.3 Population

Primed and unprimed children 6 through 35 months of age were eligible. Vaccine-primed subjects included all subjects who had previously received at least two doses of influenza vaccine, separated by 28 days. Vaccine-unprimed subjects included all subjects who had previously not received two doses of influenza vaccine, separated by at least 28 days. All subjects < 12 months of age were considered vaccine-unprimed.

All of the following criteria had to be met for inclusion:

- A male or female between, and including, 6 and 35 months of age at the time of first vaccination; children were eligible regardless of history of influenza vaccination.
- Written informed consent obtained from the parent(s) /LAR(s) of the subject.
- Subjects in stable health as determined by medical history and clinical examination before entering into the study.
- Subjects who the investigator believed that their parents/ LAR(s) could and would comply with the requirements of the protocol (e.g., safety reporting, reporting an ILI or MAV which might have included using internet, being available for follow-up contacts).

Exclusion criteria:

- Participation in a previous FLU D-QIV-004 study cohort.
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccines within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Prior receipt of any influenza vaccine (registered or investigational) within 6 months preceding the first dose of study vaccine, or planned use of such vaccines during the study period.
- Children with underlying illness who were at risk of complications of influenza and for whom yearly (seasonal) influenza vaccination was recommended in their respective country.
- Any confirmed or suspected immunosuppressive or immunodeficient condition (including HIV), based on medical history and physical examination (no laboratory testing required).
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune modifying drugs within six months prior to the first vaccine dose. For corticosteroids, this was to mean a dose equivalent to either ≥

0.5 mg/kg of body weight or maximum of 10 mg/day of prednisone or equivalent. Inhaled and topical steroids were allowed.

- Administration of immunoglobulins and/ or any blood products within 3 months preceding the first dose of study vaccine or planned administration during the study period
- Any known or suspected allergy to any constituent of influenza vaccines (including egg proteins), non-influenza vaccine comparators (including neomycin) and latex; a history of anaphylactic-type reaction to consumption of eggs; or a history of severe adverse reaction to a previous vaccination
- Any contraindication to intramuscular injection
- Acute disease and/or fever at the time of enrolment. Fever was defined as temperature ≥37.5°C by any route. Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever could be enrolled at the discretion of the investigator
- Any other condition which, in the opinion of the Investigator, prevented the subject from participating in the study

Additional criteria for children < 12 months of age:

- Prior receipt of any licensed varicella vaccine* or any licensed hepatitis A vaccine or planned use of these vaccines during the study period. Other routine registered childhood vaccinations were permitted.
  * For countries with varicella vaccine administered as 2-dose schedule, prior receipt of a single dose of a varicella vaccine was allowed if administered at least 2 weeks before the first study vaccination.
- Any history of hepatitis A or varicella diseases.

Additional criteria for children 6 - 11 months of age in countries without universal mass vaccination recommendation for pneumococcal vaccine:

- Prior receipt of any pneumococcal conjugated vaccine or planned use of this vaccine during the study

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects were randomly assigned to receive either FLU D-QIV or non-influenza vaccine comparator in a 1:1 ratio. Vaccine-primed subjects received a single 0.5 mL dose on Day 0. Vaccine-unprimed subjects received two 0.5 mL doses on Days 0 and 28. All study vaccines were administered intramuscularly (IM), except *Varilrix* which was injected subcutaneously (SC). Vaccine composition and administered doses of FLU D-QIV and each non-influenza comparator are provided in Table 5 below.

Table 5. Study FLU D-QIV-004. Study Vaccines

Vaccine Name	Active Ingredients	Excipients	Presentation	Number of doses
FLU D-QIV	15 µg HA of each of the following influenza strains: A/H1N1, A/H3N2, B/Victoria lineage, B/Yamagata lineage*	Polysorbate 80 (Tween 80), Octoxynol 10 (Triton X-100), alpha-tocopheryl hydrogen succinate, sodium chloride, (b) (4) [redacted] .	Colourless, light, opalescent fluid in monodose pre-filled syringe	1 for vaccine-primed subjects 2 for vaccine-unprimed subjects

Havrix	Hepatitis A virus strain HM175 - 720 ELISA units adsorbed on aluminum	Amino acid supplement (0.3% w/v) in a phosphate-buffered saline solution and polysorbate 20 (0.05 mg/mL); residual MRC-5 cellular proteins, formalin, and neomycin sulfate.	Homogenous, turbid, white suspension in pre-filled syringe	1 for vaccine-primed and for vaccine-unprimed subjects ≥ 12 months
*Varilrix***	Powder: Live attenuated varicella virus - $10^{3.3}$ plaque-forming units of the varicella-zoster virus Diluent: water for injection	amino acids, human albumin, lactose, neomycin sulphate, mannitol, sorbitol.	Clear peach to pink coloured solution after reconstitution	1 for vaccine-unprimed subjects ≥ 12 months
*Varivax/ ProVarivax***	Powder: Live attenuated varicella virus - 1350 plaque-forming units of Oka/Merck varicella virus Diluent: water for injection	sucrose,hydrolyzed gelatin, urea, sodium chloride, monosodium L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride.	Clear, colourless to pale yellow liquid after reconstitution	1 for vaccine-unprimed subjects ≥ 12 months
Prevnar13	13 pneumococcal capsular polysaccharides (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F), conjugated to CRM197 carrier protein and adsorbed on aluminum phosphate	(b) (4) , succinic acid and polysorbate 80.	Homogenous white suspension after shaking (in pre-filled syringe)	2 for subjects < 12 months

Source: Adapted from STN 125127/834.0: FLU D-QIV 004 Clinical Study Report; Table 7

* Strains to be included in the each vaccine were in accordance with WHO recommendations for each hemisphere and season. Refer to Table 6 of FLU D-QIV 004 Clinical Study Report for specific strains used for each cohort.

**The Varicella vaccine (*Varilrix* or *Varivax/ProVarivax*) was to be determined in function of available registered vaccine in each country.

Lot numbers for each study vaccine include the following:

- FLU D-QIV: DFLBA014A1 (Cohort 1), DFLBA018A (Cohort 2), DFLBA020B (Cohort 3 and Cohort 4), DFLBA021A (Cohort 4), AFLBA001A and AFLBA002AB (Cohort 5).
- *Havrix*: AHAVB525A (Cohort 1), AHAVB567D (Cohort 2), AHAVB603A (Cohort 3), AHAVB573F (Cohort 4), AHAVB675A (Cohort 5) and AHAVB761A (Cohort 5).
- *Varilrix*: AVARB356AZ (Cohort 1 and Cohort 2), AVARB396AZ (Cohort 2), AVARB413AZ (Cohort 3), AVARB447AY (Cohort 4), AVARB509AZ (Cohort 5), AVARB513AZ (Cohort 5), AVARB451AZ (Cohort 5) and AVARB495AZ (Cohort 5).
- *Varivax/ProVarivax*: DEXTA414AY (NPO6420) (Cohort 1), DEXTA444AY (G019895) (Cohort 3)
- *Prevnar13*: DEXTA407AZ (F08783) (Cohort 1 and Cohort 2), DEXTA412AZ (F14427) (Cohort 2), DEXTA424AZ (F40144) (Cohort 2), DEXTA407AX (F08783) (Cohort 3) DEXTA431AY (F54377) (Cohort 3 and Cohort 4), DEXTA472AZ (G59985) (Cohort 4), and DEXTA492AZ (H07583) (Cohort 5).

***Reviewer Comment**: A deficiency of the blinding procedures is apparent with the notable differences in appearance of the treatment and control vaccines, and the subcutaneous administration of Varilrix. A small number of subjects (29) were inadvertantly unblinded when they mistakenly received Varilrix via IM injection, instead of subcutaneously. It is possible that these concerns with blinding procedures affected study outcomes. In addition, Varilrix is not a US licensed vaccine, but it was accepted as a comparator in this study conducted outside of the US, for use in areas where the US licensed Varivax/ProVarivax was not available as an option for the second dose of control vaccine.*

6.1.5 Directions for Use

All subjects received a 0.5 mL dose of the assigned study vaccine(s). Vaccine-primed subjects received a single 0.5 mL dose on Day 0. Vaccine-unprimed subjects received two 0.5 mL doses on Days 0 and 28. All study vaccines were administered IM, except *Varilrix* which was administered subcutaneously (SC).

Vaccines administered IM were administered into the anterolateral region of the thigh (for children < 12 months, in general) or in the deltoid region (for children ≥ 12 months, in general). *Varilrix* was administered SC, preferably in the deltoid region.

6.1.6 Sites and Centers

The study was conducted at 106 centers in 13 countries: Bangladesh, Belgium, Czech Republic, Dominican Republic, Honduras, India, Lebanon, Philippines, Poland, Spain, Thailand, Turkey, and United Kingdom over five influenza seasons in five independent cohorts. Study Cohorts and corresponding countries and dates are described in Table 6 below.

Table 6. Study FLU D-QIV 004. Cohorts, Countries, Study Dates, and Number of subjects per cohort (Total vaccinated cohort, TVC)

Cohort	Countries	Study Dates	Number of subjects, n (TVC)
1	Belgium, Czech Republic, Poland, Spain, United Kingdom	1 October 2011 to 7 July 2012	1777
2	Bangladesh, Dominican Republic, Honduras	29 March to 12 December 2012	2526
3	Belgium, Czech Republic, Lebanon, Poland, Spain, Turkey, United Kingdom	8 October 2012 to 16 July 2013	1564
4	Bangladesh, Dominican Republic, Honduras, Philippines, Thailand	6 March to 2 December 2013	1501
5	Bangladesh, Dominican Republic, Honduras, India, Philippines, Thailand	11 March to 31 December 2014	4650

Source: Adapted from STN 125127/834.0; FLU D-QIV 004 Clinical Study Report; Tables 6, 6.13 and 22.

Reviewer Comment: *The applicant requested a deferral extension in July 2013 to ensure adequate time to enroll new subjects, thus extending the number of influenza seasons spanned by the study.*

6.1.7 Surveillance/Monitoring

Monitoring procedures for Study FLU D-QIV 004 are described in Table 7 below for vaccine-unprimed subjects and Table 8 for vaccine-primed subjects.

Table 7. Study FLU D-QIV 004. Procedures for Vaccine-unprimed Subjects

Age	6 to 35 m	~7 to 36 m	~8 to 38 m		At least 12 m
Epoch	Primary Epoch				
Type of contact	Visit 1	Visit 2	Visit 3	Surveillance contacts***	End of safety follow-up contact
Timepoint	Day 0	Day 28	Day 56	weekly	At least Day 180
Sampling time points	Pre-vacc	Post-vacc 1	Post-vacc 2	ILI / MAV follow up period	Post-vacc 2
Informed consent*	●				
Collect demographic data	●				
Collect living environment parameters	●				
Check inclusion/exclusion criteria	●				
Check elimination criteria		●	●		●
Check contraindications	●	●			
Medical history including history of recurrent AOM	●				
History of influenza and pneumococcal vaccination	●				
Physical examination	●	○	○		
Pre- and post-vaccination body temperature	●	●			
Randomisation	●				
Treatment number assignment	●	●			
Blood sampling: - for antibody determination (3.5 mL)	●**		●		
Vaccination	●	●			
Distribution of rules, thermometers and AE diary cards for solicited symptoms (Days 0-6), unsolicited AEs (Days 0-27)	○				
Training on recording of solicited symptoms and unsolicited AEs	○	○			
Daily post-vaccination recording of solicited symptoms (Days 0-6) and unsolicited AEs (Day 0-27) by subjects' parents/ LAR(s)ǂ,§	○	○			
Return of AEs diary cards, review and transcription by investigator		●	●		
Registration of the subject in the electronic surveillance system (if applicable)		○			
Training on ILI and MAV reporting		○	○		
Distribution of guidance on reporting of ILI and MAV and provision of study phones (if applicable) / booklets		○			
Surveillance contacts: weekly reminder sent on mobile phone of parent(s)/LAR(s) and/or e-mail (if applicable) or weekly contacts			○	○	
ILI and MAV reporting by parent(s)/LAR(s) ǂ,§			●	●	
Recording of non-serious AEs with medically attended visits	●	●	●	●	●
Record of concomitant medication/ vaccination	●	●	●	●	●
Reporting of SAEs, pIMDs and AEs leading to withdrawal	●$	●	●	●	●
Study conclusion and return of study phones (if applicable)					●

ILI: Influenza-like illness; MAV : medically-attended visit; AE: adverse event; SAE: serious adverse event; pIMD: potential immune mediated disease

● is used to indicate a study procedure that required documentation in the individual eCRF.

○ is used to indicate a study procedure that did not require documentation in the individual eCRF.

* in case of off site visit, RRA was to be obtained prior to written informed consent.

** blood sample was to be taken at Day 0 from subjects allocated to the immuno sub-cohort.

*** weekly surveillance for ILI and MAV was to begin 14 days post-Dose 2 and was to continue thereafter until the end of the influenza surveillance period.

$Prior to vaccination, reporting was limited to fatal SAEs and SAEs related to study participation or administration of a GSK concomitant medication.

ǂ In some countries, this procedure might have been done by subject's guardian in place of parent(s)/LAR(s) when parents were unavailable..

§ In some countries, completion of paper diary cards and/or booklets could be done with the support of field workers. If a field worker completed the diary card and/or booklet, this was to be recorded in the eCRF (as from cohort 4).

Source: STN 125127/834.0; FLU D-QIV 004 Clinical Study Report, Table 2.

Table 8. Study FLU D-QIV 004. Procedures for Vaccine-primed Subjects

Age	6 to 35 m	~ 7 to 36 m		At least 12 m
Epoch	Primary Epoch			
Type of contact	Visit 1	Visit 2	Surveillance contacts***	End of safety follow-up contact
Timepoint	Day 0	Day 28	weekly	At least Day 180
Sampling time points	Pre-vacc	Post-vacc 1	ILI / MAV follow up period	Post-vacc 1
Informed consent*	●			
Collect demographic data	●			
Collect living environment parameters	●			
Check inclusion/exclusion criteria	●			
Check elimination criteria		●		●
Check contraindications	●			
Medical history including history of recurrent AOM	●			
History of influenza and pneumococcal vaccination	●			
Physical examination	●	○		
Pre- and post-vaccination body temperature	●			
Randomisation	●			
Treatment number assignment	●			
Registration of the subject in the electronic surveillance system (if applicable)	○			
Blood sampling: - for antibody determination (3.5 mL)	●**	●		
Vaccination	●			
Distribution of rules, thermometers and AEs diary cards for solicited symptoms (Days 0-6) and unsolicited AEs (0-27)	○			
Training on recording of solicited symptoms and unsolicited AEs	○			
Daily post-vaccination recording of solicited symptoms (Days 0-6) and unsolicited AEs (Day 0-27) by subjects' parent(s)/ LAR(s) ‡, §	○			
Return of AEs diary cards, review and transcription by investigator		●		
Training on ILI and MAV reporting	○	○		
Distribution of guidance on reporting of ILI and MAV and provision of study phones (if applicable) / booklets	○			
Surveillance contacts: weekly reminder sent on mobile phone of parent(s)/LAR(s) and/or e-mail (if applicable) or weekly contacts		○	○	
ILI and MAV reporting by parent(s)/LAR(s) ‡, §		●	●	
Recording of non-serious AEs with medically attended visits	●	●	●	●
Record of concomitant medication/ vaccination	●	●	●	●
Reporting of SAEs, pIMDs and AEs leading to withdrawal	●$	●	●	●
Study conclusion and return of study phones (if applicable)				●

ILI: Influenza-like illness; MAV : medically-attended visit; AE: adverse event; SAE: serious adverse event; pIMD: potential immune mediated disease.
● s used to indicate a study procedure that required documentation in the individual eCRF.
○ is used to indicate a study procedure that didn't require documentation in the individual eCRF.
* in case of off-site visit, RRA was to be obtained prior to written informed consent.
** blood sample was to be taken for HI at Day 0 from subjects allocated to the immuno sub-cohort.
*** weekly surveillance for ILI and MAV was to begin 14 days post-Dose 1 and will continue thereafter until the end of the influenza surveillance period.
$ Prior to vaccination, reporting is limited to fatal SAEs and SAEs related to study participation or administration of a GSK concomitant medication
‡ In some countries, this procedure might be done by subject's guardian in place of parent(s)/LAR(s) when parents are unavailable..
§ In some countries, completion of paper diary cards and/or booklets could be done with the support of field workers. If a field worker completed the diary card and/or booklet, this was to be recorded in the eCRF (as from cohort 4).

Source: STN 125127/834.0; FLU D-QIV 004 Clinical Study Report,Table 3.

6.1.8 Endpoints and Criteria for Study Success

Study FLU D-QIV 004, the two parallel primary endpoints and the criteria for success for each of these primary endpoints were as follows:

- First occurrence of RT-PCR confirmed moderate to severe influenza A and/or B disease due to any seasonal influenza strain during the influenza surveillance period with criteria for success defined as if the lower limit (LL) of the two-sided 97.5% Confidence Interval (CI) of vaccine efficacy (VE) was above 25%.
- First occurrence of RT-PCR confirmed influenza A and/or B disease of any severity due to any seasonal influenza strain during the influenza surveillance period with criteria for success defined as if the LL of the two-sided 97.5% CI of VE was above 15%.

The seven secondary efficacy endpoints and their criteria success for study FLU D-QIV 004 are as follows below. They were evaluated sequentially with an alpha level of 2.5% (one-sided, or 95% CI).
During the influenza surveillance period, the first occurrence of:

1. LRI with RT-PCR confirmed influenza A and/or B infection due to any seasonal influenza strain with success demonstrated if the LL of the two-sided 95% CI of VE was above 15%.
2. Culture-confirmed moderate to severe influenza A and/or B disease due to antigenically-matching influenza strains with success demonstrated if the LL of the two-sided 95% CI of VE was above 15%.
3. Culture-confirmed influenza A and/or B disease of any severity due to antigenically-matching influenza strains with success demonstrated if the LL of the two-sided 95% CI of VE was above 15%.
4. Culture-confirmed moderate to severe influenza A and/or B disease due to any seasonal influenza strain with success demonstrated if the LL of the two-sided 95% CI of VE was above 15%.
5. Culture-confirmed influenza A and/or B disease of any severity due to any seasonal influenza strain with success demonstrated if the LL of the two-sided 95% CI of VE was above 10%.
6. AOM with RT-PCR confirmed influenza A and/or B infection due to any seasonal influenza strain with success demonstrated if the LL of the two-sided 95% CI of VE was above 10%.
7. RT-PCR confirmed severe influenza A and/or B due to any seasonal influenza strain with success demonstrated if the LL of the two-sided 95% CI of VE was above 15%.

Reviewer Comment*: All of these primary and secondary endpoints were modified during the study period. The sequential order of the secondary endpoints were changed and endpoint #3 was a primary endpoint initially. Refer to Section 2.5 for discussion of primary endpoint modifications*

There was one secondary immunogenicity endpoint which was to evaluate the humoral response in terms of HI antibody response against each of the four strains contained in FLU D-QIV 28 days after completion of vaccination, in an immuno sub-cohort of subjects.

The safety endpoints were as follows:

- Solicited local and general symptoms:

  - Occurrence, intensity, and duration of each local solicited AE within 7 days (Day 0-6) after each vaccination.
  - Occurrence, intensity, duration and relationship to vaccination of each general solicited AE within 7 days (Day 0-6) after each vaccination.
- Unsolicited AEs:
  - Occurrence, intensity and relationship to vaccination of unsolicited AEs within 28 days (Day 0-27) after each vaccination.
- AEs with Medically Attended Visit (MAV):
  - Occurrence, intensity and relationship to vaccination of AEs with MAV during the entire study period.
- SAEs:
  - Occurrence and relationship to vaccination of SAEs during the entire study period.
- Potential Immune-Mediated Disease (pIMD):
  - Occurrence, intensity and relationship to vaccination of pIMDs during the entire study period.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Primary and secondary hypotheses and endpoints are described above in Section 6.1.8.

The total target sample size of the study was approximately 10,500-12,000 subjects between 6 and 35 months of age, randomized 1:1 between the FLU D-QIV and the control group (receiving a U.S. licensed pneumococcal polysaccharide conjugated vaccine in children aged <12 months or a U.S licensed inactivated hepatitis A vaccine / a licensed varicella virus vaccine in children ≥12 months).

Based on the assumption of a true vaccine efficacy (VE) of 55% for prevention of RT-PCR confirmed moderate to severe influenza disease, 240 cases of RT-PCR confirmed moderate to severe influenza disease would be needed to demonstrate 93% power that the lower limit (LL) of the two-sided 97.5% confidence interval (CI) for the vaccine efficacy (VE) is above 25%. Based on the assumption of a true VE of 35% for prevention of RT-PCR confirmed influenza of any severity, a total of 702 cases would be needed to demonstrate 90% power that the LL of the two-sided 97.5% CI for VE is above 15%

Assuming a 9% attack rate of any influenza in the control group, an attack rate of 3.5% of moderate to severe influenza in the control group, and assuming that 10% of subjects would not be evaluable, the sample size of 10,500-12,000 would be required to meet the primary objectives.

Global power for evaluation of both primary objectives is approximately 84%.

Please see the statistical review for detailed description of the statistical analysis.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Below are the definitions of each population that was analyzed.

Total vaccinated cohort (TVC)
The total vaccinated cohort (TVC) included all subjects with at least one documented vaccine administration. Thus the safety analysis was based on the TVC included all vaccinated subjects and the immunogenicity analysis was based on the TVC for whom immunogenicity data was available. The TVC analysis was performed per treatment actually administered (at dose 1). The TVC consisted of 12018 subjects (6006 in the FLU D-QIV group and 6012 in the control group).

According to protocol cohort for analysis of efficacy – time to event (ATP-E-Time to event)
The ATP-E-Time to event cohort included all eligible subjects from the TVC with completed scheduled vaccination who met all inclusion and exclusion criteria for the study, who had received study vaccine(s) according to their random assignment, for whom administration site of study vaccine was known, and who started their influenza surveillance period. Subjects who met criteria for elimination or exclusion from the ATP analysis were censored at the time of the occurrence of the event and were not eliminated. The ATP-E - Time to event cohort consisted of 11404 subjects (5707 in the FLU D-QIV group and 5697 in the control group). The ATP-E-time to event cohort consisted of 11404 subjects (5707 in the FLU D-QIV group and 5697 in the control group). Out of the 1332 subjects in the ATP cohort for immunogenicity, 1594 subjects (59 FLU D-QIV and 73 control) were enrolled from Cohort 1, 2383 (1188 FLU D-QIV and 1195 control) from Cohort 2, 1439 subjects (718 FLU D-QIV and 721 control) from Cohort 3, 1445 subjects (725 FLU D-QIV and 720 control) from Cohort 4, and 4543 subjects (2283 FLU D-QIV and 2260 control) from Cohort 5.

According to protocol cohort for analysis of immunogenicity (ATP)
The ATP cohort for analysis of immunogenicity included all evaluable subjects from the TVC (i.e., who completed the scheduled vaccination, met all eligibility criteria, who received study product according to their random assignment, who complied with the procedures and intervals defined in the protocol, who did not meet any elimination or exclusion criteria) for whom data concerning immunogenicity endpoint measures were available. This included subjects for whom assay results were available for HI antibodies against at least one study vaccine strain after vaccination. The ATP cohort for immunogenicity consisted of 1332 subjects (753 in the FLU D-QIV group and 579 in the control group). Out of the 1332 subjects in the ATP cohort for immunogenicity, 132 subjects (59 FLU D-QIV and 73 control) were enrolled from Cohort 1, 538 (353 FLU D-QIV and 185 control) from Cohort 2, 120 subjects (66 FLU D-QIV and 54 control) from Cohort 3, 241 subjects (127 FLU D-QIV and 114 control) from Cohort 4, and 301 subjects (148 FLU D-QIV and 153 control) from Cohort 5.

6.1.10.1.1 Demographics
Table 9 displays the demographics for the TVC.

Table 9. Study FLU D-QIV 004. Subject Demographics (Total Vaccinated Cohort)

		Fluarix QIV N=6006		**Control** N=6012		**Total** N= 12018	
Characteristics	**Parameters/Categories**	Value or n	%	Value or n	%	Value or n	%
Age (months) at first vaccination	Mean	21.9	-	21.8	-	21.9	-
	SD	8	-	-	-	-	-
	Median	22	-	22	-	22	-
	Minimum	6	-	6	-	6	-
	Maximum	35	-	43	-	43	-
Gender	Female	2933	48.8	2925	48.7	5858	48.7
	Male	3073	51.2	3087	51.3	6160	51.3
Ethnicity	Asian	2727	45.4	2719	45.2	5446	45.3
	White	1613	26.9	1631	27.2	3244	27
	Other	1666	27.7	1662	27.6	3328	27.7

Source: Adapted from STN 125127/834.0; FLU D-QIV 004 Clinical Study Report, Table 27.

***Reviewer Comment**: The study demographics show that age, gender and ethnicity are balanced between the treatment groups. The ethnicity breakdown is reflective of the countries in which the study was conducted.*

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

6.1.10.1.3 Subject Disposition
Subject disposition is depicted in Table 10 below.

Table 10. Study FLU D-QIV 004. Number of subjects vaccinated, completed and withdrawn with reasons of withdrawal (Total vaccinated cohort)

	D-QIV	**Control**	**Total**
Number of subjects vaccinated	6006	6012	12018
Number of subjects completed, n (%)	5808 (96.7)	5804 (96.5)	11612 (96.6)
Number of subjects withdrawn, n (%)	198 (3.2)	208 (3.5)	406 (3.4)
Reasons for Withdrawal			
Serious Adverse Event	1	6	7
Non-Serious Adverse Event	3	10	13
Protocol Violation	1	0	1
Consent withdrawal	140	129	269
Migrated/moved from study area	20	23	43
Lost to follow up (incomplete vaccination course)	6	16	22
Lost to follow up (complete vaccination course)	17	19	36
Sponsor Study Termination	0	0	0
Others	0	5	15

Source: STN 125127/834.0; FLU D-QIV 004 Clinical Study Report, Table 23.
D-QIV = Subjects who received the FLU D-QIV Vaccine
Control = Subjects who received the Control vaccine (*Havrix/Varivax/ProVarivax/Varilrix/Prevnar13*)

Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come back for the last visit

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary efficacy endpoints for prevention of RT-PCR confirmed moderate to severe influenza A and/or B disease and RT-PCR confirmed influenza A and/or B of any severity both met pre-specified statistical success criteria.

The vaccine efficacy (VE) for the prevention of RT-PCR confirmed moderate to severe influenza A and/or B disease due to any seasonal strain in comparison to non-influenza vaccine controls in children 6 through 35 months was 63.2%; the lower limit (LL) of the two-sided 97.5% confidence interval (CI) was 51.8%, which met the pre-specified criterion of >25%. Refer to Table 11 below.

The VE for prevention of RT-PCR confirmed influenza A and/or B disease of any severity due to any seasonal strain, when compared to non-influenza vaccine controls in children 6 through 35 months, was 49.8 %; LL of the two-sided 97.5% CI was 41.8%, which met the pre-specified criterion to demonstrate efficacy of >15%. Refer to Table 11 below.

Table 11. Study FLU D-QIV 004. Attack Rates and Vaccine Efficacy against Influenza A and/or B in Children Aged 6 through 35 months (ATP Cohort for Efficacy – Time to Event)

			Attack Rates (n/N)	Vaccine Efficacy		
	N[1]	N[2]	%	%	LL	UL
RT-PCR-Confirmed Influenza with Adverse Outcomes						
FLUARIX QUADRIVALENT	5,707	85	1.49	64.6	53.2[3]	73.5
Non-Influenza Comparator[4,5]	5,697	237	4.16	-	-	-
All RT-PCR-Confirmed Influenza of Any Severity						
FLUARIX QUADRIVALENT	5,707	344	6.03	49.8	41.8[3]	56.8
Non-Influenza Comparator[4,5]	5,697	662	11.62	-	-	-

Source: Adapted from STN 125127/834.6 module 1.11.3 Clinical Information Amendment

[1] Number of subjects in the ATP cohort for efficacy – time to event, which included subjects who met all eligibility criteria, who were followed for efficacy and complied with the study protocol until the influenza-like episode.
[2] Number of subjects who reported at least one case in the reporting period.
[3] Vaccine efficacy for FLUARIX QUADRIVALENT met the pre-defined criterion for the lower limit of the 2-sided 97.5% CI (>25% for influenza associated with adverse outcomes, and >15% for all influenza).
[4] Children younger than 12 months: pneumococcal 13-valent conjugate vaccine [Diphtheria CRM197 Protein] (Wyeth Pharmaceuticals, Inc.).
[5] Children 12 months and older: HAVRIX (Hepatitis A Vaccine) for those with a history of influenza vaccination; or HAVRIX (Dose 1) and a varicella vaccine (U.S. Licensed Manufactured by Merck & Co., Inc. or Non-U.S. Licensed Manufactured by GlaxoSmithKline Biologicals) (Dose 2) for those with no history of influenza vaccination.

Among subjects with RT-PCR-positive influenza A and/or B disease, subjects were further prospectively classified based on the presence of adverse outcomes associated with influenza infection: fever >102.2°F, physician-diagnosed acute otitis media, physician-diagnosed lower respiratory tract illness, physician-diagnosed serious extra-pulmonary complications, hospitalization in the intensive care unit, or supplemental oxygen required for more than 8 hours. The incidence of adverse outcomes associated with RT-PCR positive influenza is presented below in Table 12.

Table 12. Study FLU D-QIV 004. Incidence of Adverse Outcomes Associated with RT-PCR-Positive Influenza in Children Aged 6 through 35 Months (ATP Cohort for Efficacy- Time to Event)

Influenza Associated Symptom[3]	D-QIV[1] N=5,707			Control[2] N=5,697		
	Number of Events	Number of Subjects[4]	%	Number of Events	Number of Subjects[4]	%
Fever >39^{0}C	62	61	1.1	184	183	3.2
Physician diagnosed AOM	5	5	0.1	15	15	0.3
Physician diagnosed LRI[5]	28	28	0.5	62	61	1.1
Physician diagnosed serious extra-pulmonary complication of influenza[6]	2	2	0	3	3	0.1
Hospitalization in the Intensive Care Unit (ICU)	0	0	0	0	0	0
Supplemental oxygen requirement for > 8 hrs	0	0	0	0	0	0

Source: STN 125127/834.8 module 1.14 Labeling.
[1] D-QIV = Subjects who received the FLU D-QIV Vaccine
[2] Control = Subjects who received the Control vaccine (*Havrix/Varivax/ProVarivax/Varilrix/Prevnar13*)
[3] Subjects who experienced more than one adverse outcome, each outcome was counted in the respective category
[4] Number of subjects with at least one event in a given category
[5] Pneumonia, lower respiratory tract infection, bronchiolitis, bronchitis, or croup infection as per final diagnosis by physician.

[6] Includes myositis, encephalitis or other neurologic condition including seizure, myocarditis/pericarditis or other serious medical condition as per final diagnosis by physician.

***Reviewer Comment**: As previously noted, this composite definition of moderate to severe influenza included a wide range of adverse outcomes associated with influenza, ranging from fever >39 ^{0}C to hospitalization requiring supplemental oxygen. The majority of subjects classified with "moderate to severe influenza" had fever >39 ^{0}C alone without additional adverse outcomes, and there were 5 total subjects with "severe influenza" (all with physician diagnosed extra-pulmonary complication of influenza, and none with hospitalization in the ICU or supplemental oxygen requirement for >8 hours) thus this classification of moderate to severe influenza in this study primarily indicates that subjects with confirmed influenza also had a fever >39 ^{0}C.*

6.1.11.2 Analyses of Secondary Endpoints

The VE of FLU D-QIV for the prevention of culture confirmed influenza A and/or B of any severity due to antigenically-matching influenza strains was 60.1 %.

***Reviewer Comment**: In this reviewer's opinion, this secondary endpoint is the most informative for vaccine efficacy and indicates that FLU D-QIV is efficacious for prevention of influenza caused by the influenza strains contained in the vaccine.*

The first six of the seven sequential secondary endpoints met the pre-specified statistical criteria. See Table 13 below for vaccine efficacy results of all seven secondary endpoints.

Table 13. Study FLU D-QIV 004. Vaccine Efficacy for the Seven Secondary Endpoints (ATP cohort for efficacy – time to event)

				Attack Rate	Vaccine Efficacy		
						95% CI	
Event Type	**Group**	**N[1]**	**n[2]**	**%**	**%**	**LL**	**UL**
RT-PCR confirmed influenza - LRI	D-QIV[3]	5707	28	0.49	54.0	28.9[4]	71.0
	Control[5]	5697	61	1.07	-	-	-
Vaccine matching culture confirmed influenza – with adverse outcomes associated with influenza infection	D-QIV	5707	20	0.35	77.6	64.3[4]	86.6
	Control	5697	88	1.54	-	-	-
Vaccine matching culture confirmed influenza – any severity	D-QIV	5707	88	1.54	60.1	49.1[4]	69.0
	Control	5697	216	3.79	-	-	-
Culture confirmed influenza – with adverse outcomes associated with influenza infection	D-QIV	5707	79	1.38	63.8	53.4[4]	72.2
	Control	5697	216	3.79	-	-	-
Culture confirmed influenza – any severity	D-QIV	5707	303	5.31	51.2	44.1[6]	57.6
	Control	5697	602	10.57	-	-	-
RT- PCR confirmed influenza – AOM	D-QIV	5707	12	0.21	56.6	16.7[6]	78.8
	Control	5697	28	0.49	-	-	-
RT-PCR confirmed influenza - Severe	D-QIV	5707	2	0.04	34.2	-297.3[4]	91.3
	Control	5697	3	0.05	-	-	-

Source: Adapted from STN 125127/834.0; FLU D-QIV 004 Clinical Study Report, Table 39.
[1] N = number of subjects in each group
[2] n = number of subjects who reported at least one event in the reporting period
[3] D-QIV = subjects who received the FLU D-QIV Vaccine
[4] Success demonstrated if the LL of the two-sided 95% CI of VE was above 15%.
[5] Control = subjects who received the Control vaccine (*Havrix/Varivax/ProVarivax/Varilrix/Prevnar13*)
[6] Success demonstrated if the LL of the two-sided 95% CI of VE was above 10%.

Reviewer Comment: *The first six of these seven secondary endpoints met the pre-defined success criteria and they each assess a different aspect of laboratory confirmed influenza infection in the same subject population. There were too few cases of protocol defined severe influenza (physician diagnosed extra-pulmonary complication of influenza, hospitalization in the ICU, or supplemental oxygen requirement for >8 hours) for the seventh endpoint to be informative, and the endpoint was not met.*

A summary of immunogenicity by HI antibody Geometric Mean Hemagglutination Inhibition Antibody Titers (GMT) against influenza vaccine strains and Seroconversion rates (SCR) are displayed below in Table 14.

Table 14. Study FLU D-QIV 004. Geometric Mean Hemagglutination Inhibition Antibody Titers Against Influenza Vaccine Strains and Seroconversion rates 28 days after Last Vaccination (ATP cohort for immunogenicity)

		GMT[1]		SCR[2]	
Influenza Strain	Group	N[3]	Value	N	n (%)[4]
Flu A (H1N1) HI	D-QIV[5]	752	165.3	743	596 (80.2)
	Control[6]	578	12.6	566	20 (3.5)
Flu A (H3N2) HI	D-QIV	753	132.1	746	513 (68.8)
	Control	578	14.7	567	24 (4.2)
Flu B (Victoria) HI	D-QIV	750	92.6	742	514 (69.3)
	Control	579	9.2	567	5 (0.9)
Flu B (Yamagata) HI	D-QIV	753	121.4	745	605 (81.2)
	Control	579	7.6	568	13 (2.3)

Source: Adapted from STN 125127/834: FLU D-QIV 004 Clinical Study Report, Table 61.
[1] GMT: geometric mean antibody titer calculated on all subjects
[2] Seroconversion rate (SCR) defined as:
For initially seronegative subjects, antibody titer ≥ 40 1/DIL at post-vaccination
For initially seropositive subjects, antibody titer at post-vaccination ≥ 4-fold the pre-vaccination antibody titer
[3] Number of subjects with results available; for SCR, both pre and post results
[4] n/%:number/percentage of seroconverted subjects
[5] D-QIV = Subjects who received the FLU D-QIV Vaccine
[6] Control = Subjects who received the Control vaccine (*Havrix/Varivax/Varilrix/ProVarivax/Prevnar13*)

Reviewer Comment*: These immunogenicity data are pooled across all cohorts and are strain specific for each cohort. Comparison of GMT's and SCR's in each cohort had comparable results as the ATP cohort for immunogenicity. Because more than 5% of*

subjects were excluded from the primary ATP cohort for immunogenicity analysis, an additional analysis was performed on the total vaccinated cohort (TVC); results for the TVC were comparable to those obtained for the ATP cohort for immunogenicity.

6.1.11.3 Subpopulation Analyses

The study was not powered to detect differences in efficacy, immunogenicity or safety with regard to gender or geographical ancestry. Post-hoc analyses suggested efficacy, immunogenicity and safety to be comparable across both genders and across geographic ancestry (White/Caucasian, Asian, Others) for children 6 through 35 months of age.

In general, vaccine efficacy and immunogenicity were lower in the subgroup of children 6 through 11 months of age; however, the study was not powered to detect significant differences in age and this age group had the lowest number of enrolled subjects when compared to those in the 6 through 17 month or 18 through 35 month age groups.

Vaccine efficacy for RT-PCR confirmed influenza with adverse outcomes by cohort ranged from 42.8% in Cohort 1, 71.1% in Cohort 2, 83.9% in Cohort 3, 52.2% in Cohort 4, to 61.9% in Cohort 5. Vaccine efficacy for RT-PCT confirmed influenza of any severity by cohort ranged from 57.8% in Cohort 1, 31.2% in Cohort 2, 73.4% in Cohort 3, 30.3% in Cohort 4, to 41.4% in Cohort 5.

Reviewer Comment: *These subpopulation vaccine efficacy analyses by cohort likely reflect the expected variability of circulating influenza virus strains and vaccine virus strains for the geographic area of each cohort.*

6.1.11.4 Dropouts and/or Discontinuations

There were a total of 406 subjects who withdrew from the study and the numbers and reasons for withdrawal were balanced between the FLU D-QIV and control groups. The applicant used the data available until the date of withdrawal for analysis.

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety and reactogenicity data was collected and analyzed for the total vaccinated cohort (TVC), as defined in section 6.1.10.1. Solicited local and general adverse events (AEs) to evaluate reactogenicity were collected on diary cards for 7 days after each vaccination and unsolicited symptoms were collected for 28 days after each vaccination. Medically attended events, serious adverse events, and potential immune mediated disorders to evaluate safety were collected during the entire study period, which was 6 to 8 months, depending on date of enrollment.

6.1.12.2 Overview of Adverse Events/Reactions

At least one Adverse Event (AE) (any solicited or unsolicited, local or general) was reported within 7 days post-vaccination for 51.8% and 53.8% of subjects in the FLU D-QIV and control groups, respectively. At least one grade 3 AE was reported for 6% and 6.2% of subjects in the FLU D-QIV and control groups, respectively.

Local solicited Adverse Reactions within 7 days post-vaccination:

Injection site pain was the most frequently reported solicited local Adverse Reaction (AR) (22.9% and 23.3% of subjects in the FLU D-QIV and control groups, respectively). Grade 3 injection site pain was reported for 0.7% and 0.8% of subjects overall in the FLU D-QIV and control groups respectively. (Table 15 below)

After Dose 1, the incidence of injection site pain was 17.2% and 17.8% of subjects in the FLU D-QIV and control groups, respectively. After Dose 2, the incidence of injection site pain was 14% and 14.2% of subjects in the FLU D-QIV and control groups, respectively.

Redness at the injection site after Dose 1 was reported for 13.1% and 14.1% of subjects in the FLU D-QIV and control groups, respectively. There were no reports of Grade 3 redness in either group. Swelling at the injection site after Dose 1 was reported in 7.9% and 8.8% of subjects in the FLU D-QIV and control groups, respectively. There was one report of Grade 3 swelling in the FLU D-QIV group and none in the control group.

***Reviewer Comment**: The rates of solicited local adverse reactions for the control vaccines (Prevar13, Havrix, Varivax/ProVarivax or Varilrix) are comparable to the data available in their respective package inserts for pediatric age groups, which is reassuring with regard to the conduct of this study.*

Table 15. Study FLU D-QIV 004. Solicited Local Adverse Reactions by Type and Maximum Severity Occurring within 7 Days of Vaccination with Dose 1 (Total Vaccinated Cohort)

Subjects experiencing at least one local adverse reaction by maximum intensity	FLU D-QIV N[1]=5899 n[2] (%)	Control N=5896 n (%)
Pain: Total	1015 (17.2)	1047 (17.8)
Grade 2[3] or 3[4]	190 (3.2)	190 (3.2)
Grade 3	23 (0.4)	30 (0.5)
Medical Advice	2 (0)	2 (0)
Redness: Total	775 (13.1)	831 (14.1)
> 20 mm	10 (0.2)	12 (0.2)
> 50 mm	1 (0)	0 (0)
Medical Advice	3 (0.1)	3 (0.1)
Swelling: Total	467 (7.9)	518 (8.8)
> 20 mm	26 (0.4)	19 (0.3)
> 50 mm	0 (0)	0 (0)
Medical Advice	2 (0)	3 (0.1)

Source: Adapted from STN 125127/834.0: Clinical Study Report FLU D-QIV 004, Table 74.
[1]N: total number of subjects
[2]n: number of subjects per group
[3]Grade 2: cries/protests on touch
[4]Grade 3: cries when limb is moved/spontaneously painful

Systemic solicited ARs within 7 days post-vaccination:
Overall, the most frequently reported solicited general AR was irritability/fussiness (23.4% and 24.2% of subjects in the FLU D-QIV and control groups, respectively), followed by loss of appetite (20.8% and 21.8% subjects in the FLU D-QIV and control groups, respectively), and drowsiness (17.3% and 19.1% subjects in the FLU D-QIV and

control groups, respectively). Grade 3 irritability/fussiness was reported for 0.7 and 1.1% of subjects in the FLU D-QIV and control groups, respectively. Grade 3 loss of appetite was reported for 1.9% and 1.6% of subjects in the FLU D-QIV and control groups, respectively. Grade 3 drowsiness was reported for 1% and 1.2% of subjects in the FLU D-QIV and control groups, respectively.

The most frequently reported solicited grade 3 general AR related to vaccination within 7 post-vaccination was fever (> 39^0C), reported for 1.3% and 1.4% of subjects in the FLU D-QIV and control groups, respectively.

After Dose 1, the incidence of irritability/fussiness was 16.2% and 17.5% of subjects in the FLU D-QIV and control groups, respectively (Table 16). After Dose 2, the incidence of irritability/fussiness was 13.5% of subjects in both the FLU D-QIV and control groups.

***Reviewer Comment**:The rates of solicited general adverse reactions for the control vaccines (Prevar13, Havrix, Varivax/ProVarivax or Varilrix) are comparable to the data available in their respective package inserts for pediatric age groups, which is reassuring with regard to the conduct of this study.*

Table 16. Study FLU D-QIV 004. Solicited General Adverse Reactions by Type and Maximum Severity Occurring within 7 Days of Vaccination with Dose 1 (Total Vaccinated Cohort)

Subjects experiencing at least one general adverse reaction by maximum intensity	FLU D-QIV N[1]=5899 n[2] (%)	Control N=5896 n (%)
Drowsiness: Total	739 (12.5)	829 (14.1)
Grade 2 or 3[3]	177 (3)	206 (3.5)
Grade 3	39 (0.7)	59 (0.9)
Medical Advice	21 (0.4)	32 (0.5)
Irritability/Fussiness: Total	955 (16.2)	1029 (17.5)
Grade 2 or 3[4]	249 (4.2)	292 (5)
Grade 3	42 (0.7)	62 (1.1)
Medical Advice	38 (0.6)	44 (0.7)
Loss of Appetite: Total	847 (14.4)	872 (14.8)
Grade 2 or 3[5]	227 (3.8)	254 (4.3)
Grade 3	68 (1.2)	60 (1)
Medical Advice	47 (0.8)	39 (0.7)
Fever: Total	390 (6.6)	438 (7.4)
≥38^0C	372 (6.3)	425 (7.2)
>38.5^0C	160 (2.7)	194 (3.3)
>39^0C	78 (1.3)	76 (1.3)
>39.5^0C	29 (0.5)	36 (0.6)
>40^0C	3 (0.1)	8 (0.1)
Medical Advice	85 (1.4)	106 (1.8)

Source: Adapted from STN 125127/834.0: Clinical Study Report FLU D-QIV 004, Table 75.
[1]N: total number of subjects
[2]n: number of subjects per group
[3]Grade 2: interferes with normal activity, Grade 3: prevents normal activity
[4]Grade 2: crying more than usual/interferes with normal activity, Grade 3: Crying that

cannot be comforted/prevents normal activity
[5]Grade 2: eating less than usual/interferes with normal activity, Grade 3: not eating at all.

Unsolicited AEs:
During the 28 day post-vaccination period, at least one unsolicited AE was reported for 44% and 44.6% of subjects in the FLU D-QIV and control groups, respectively. Grade 3 unsolicited AEs were reported for 2.7% and 2.5% of subjects in the FLU D-QIV and control groups, respectively. Nasopharyngitis (14.5% and 15.7% of subjects in the FLU D-QIV and control groups, respectively) and upper respiratory infection (8.7% and 8.6% of subjects in the FLU D-QIV and control groups, respectively) were the most frequently reported unsolicited AEs.

MAVs:
At least one unsolicited AE with a medically attended visit (MAV) during the entire study period was reported for 64.7% and 66.3% of subjects in the FLU D-QIV and control groups, respectively. The most frequently reported unsolicited AEs with MAV were nasopharyngitis (29.0% and 30.0% of subjects in the FLU D-QIV and Control groups, respectively). Grade 3 unsolicited AEs with MAV during the entire study were reported for 3.3% (FLU D-QIV) and 3.5% (Control) of subjects.

***Reviewer Comment**: Local and general solicited reactions, unsolicited AEs, and MAVs were balanced between the treatment arms. These were all known reactions that are in Section 6 of the package insert.*

6.1.12.3 Deaths

Four subjects experienced a total of six SAEs associated with a fatal outcome. One subject was in the FLU D-QIV group and the other three were in the control group. None of the SAEs with fatal outcome were attributed to the study vaccine.

The subject in the FLU D-QIV group and two subjects in the control group died due to drowning. The final subject in the control group with fatal outcome died due to respiratory failure and septic shock from complications of bronchitis, pneumonia and pleural effusion (b) (6) days after the second dose of control vaccine (Prevnar13).

***Reviewer Comment**: The case narratives support the investigator's and this reviewer's assessment that these fatal outcomes were not attributable to the study vaccines. The single death in the FLU D-QIV group was due to drowning and not attributable to the vaccine.*

6.1.12.4 Nonfatal Serious Adverse Events

During the entire study period, at least one SAE was reported for 217 (3.6%) of subjects in the FLU D-QIV group and for 201 (3.3%) of subjects in the control group.

There were 7 SAEs in 6 subjects in the FLU D-QIV group considered possibly related to vaccination by the investigator. These SAEs included the following: 1 subject with immune thrombocytopenia purpura (ITP) 21 days after 2nd dose of vaccine, 1 subject with hypersensitivity within 7 hours of first dose of vaccine, 1 subject with facial paralysis 8 days after 1st dose of vaccine, 1 subject with nephrotic syndrome 13 days after the 2nd dose of vaccine, 1 subject with apnea and febrile convulsion 10 days after first dose vaccine and 1 subject with febrile convulsion 2 days after the first dose of vaccine.

In the control group, there were 2 SAEs in 2 subjects with possible causal relationship to vaccination: 1 subject with febrile convulsion 2 hours after the 2nd dose of *Prevnar13* and 1 subject with anoxic seizures 49 days after the 2nd study vaccine (*Varivax*).

Reviewer Comment*: The case narratives support the investigator's and this reviewer's assessments of possible relatedness to the study vaccines. In this reviewer's opinion, these do not represent a new safety signal. Hypersensitivity, facial paresis and convulsion are reactions already included in Section 6.2 of the product package insert. Nephrotic syndrome and ITP were events that occurred following the second dose of vaccine without an obvious biologically plausible link to vaccination.*

6.1.12.5 Potential Immune-Mediated Diseases (pIMDs)

At least one pIMD was reported for 5 subjects in the FLU D-QIV group. There were no reports of pIMDs for the control group.

One subject had 3 SAEs reported that were classified as pIMDs: nephrotic syndrome that began 13 days after 2nd dose of FLU D-QIV, followed by anaphylactic shock 10 minutes into intravenous gammaglobulin administration, and venous thrombosis at the site of a dialysis catheter during his hospitalization. The nephrotic syndrome was considered possibly related to the vaccine, however not the anaphylaxis and venous thrombosis which were thought to be iatrogenic events that occurred during hospitalization.

One subject developed ITP 21 days after the 2nd dose of FLU D-QIV that eventually resolved without platelet transfusion. The investigator considered that it was possible that the ITP was due to a bacterial or viral infection, however could not rule out the FLU D-QIV vaccine as a possible cause.

One subject was diagnosed with Bell's palsy 8 days after 1st dose of FLU D-QIV. She received the 2nd dose of FLU D-QIV without worsening and the Bell's palsy resolved 10 weeks after onset. This was considered by the study investigator to be possibly related to the vaccine.

The last two subjects with reported pIMDs were not considered by the study investigator to be possibly related to FLU D-QIV. One subject was diagnosed with Celiac disease 206 days after the 2nd dose of FLU D-QIV. The other subject developed facial paralysis 33 days after 1st dose of FLU D-QIV with preceding fever, ear pain, and upper respiratory tract infection diagnosed as non-specific viral infection. The facial palsy resolved 2 months later.

Reviewer Comment*: The case narratives provided support the investigator's assessments of possible relatedness to the study vaccine for the first 3 subjects, as well as less likely relatedness for the last two subjects. Given the small number of subjects affected and that these are generally rare events, it is difficult to make definitive conclusions about causality. These are also conditions that can occur in the general pediatric population and is within the background rate of each event among the general pediatric population.*

6.1.12.6 Clinical Test Results

No laboratory or other clinical testing was routinely performed for safety monitoring purposes.

6.1.12.7 Dropouts and/or Discontinuations

A total of 13 subjects (3 in the FLU D-QIV group and 10 in the control group) prematurely withdrew from the study because of a non-serious AE. One of these in the FLU D-QIV group was assessed by the study investigator as possibly related to the vaccination: an upper respiratory infection 2 days after the 2nd dose of vaccine, from which the subject full recovered.

A total of 7 subjects (1 in the FLU D-QIV group and 6 in the control group) prematurely withdrew from the study because of an SAE (FLU D-QIV group: drowning; Control groups: 3 drowning, 1 dehydration, 1 gastrointestinal disorder, 1 pneumonia/tuberculosis, 1 pneumonia/bronchioitis/pleural effusion). None of these were assessed as possibly related to vaccination by the investigator.

Reviewer Comment*: The case narratives provided support the investigator's assessments of relationship (possibly related for the URI and unrelated for the drowning) to the study vaccination as described above.*

6.1.13 Study Summary and Conclusions

Study FLU D-QIV 004 was a Phase 3, randomized, non-influenza comparator controlled, multi-country, multi-center, observer blind study conducted in 13 countries over five influenza seasons in different geographical regions (Asia, Europe, Central America) that enrolled 12,018 subjects to evaluate the absolute efficacy, safety and immunogenicity of FLU D-QIV as compared to non-influenza vaccine controls in children 6 through 35 months of age. The demographic characteristics were similar between the 2 treatment groups.

Of the 12,018 subjects enrolled, 6006 received FLU D-QIV and 6012 received a non-influenza vaccine control (*Prevnar13, Havrix, and/or Varilrix/Varivax/ProVarivax*, depending on age). Vaccine-primed subjects received a single IM dose of study vaccine whereas vaccine-unprimed subjects received 2 doses 28 days apart. All subjects <12 months of age were considered vaccine-unprimed.

The primary efficacy objectives were prevention of RT-PCR confirmed influenza A and/or B disease (with adverse outcomes associated with influenza infection or of any severity) due to any seasonal influenza strain, when compared to non-influenza controls. The pre-specified criteria for efficacy of FLU D-QIV as compared to the non-influenza vaccine controls were met for both primary objectives.

The secondary endpoint for vaccine efficacy was demonstrated for all influenza strains contained in the vaccine for FLU D-QIV compared to non-influenza vaccine controls with a vaccine efficacy of 60.1%.

Local and systemic reactogenicity, including fever and rates of grade 3 AEs, and medically attended AEs were balanced between treatment arms. There were 3 subjects in the FLU D-QIV group and 10 in the control group who withdrew from the study due to a non-serious AE, and one subject in the FLU D-QIV group and 6 in the control group

who withdrew due to a serious AE. One non-serious AE (upper respiratory tract infection in the FLU D-QIV group) had a possible causal relationship to the vaccination. None of the SAEs leading to study withdrawal were assessed as related to the vaccinations. There were 5 subjects with pIMDs and 3 events were considered possibly related to vaccination in the FLU D-QIV group (one case each of ITP, nephrotic syndrome, and Bell's palsy). None of these safety data indicate that there is a new safety concern in this age group.

The efficacy, immunogenicity and safety data support the use of FLU D-QIV in persons ages 6 months through 35 months.

6.2 Study #2 FLU-D-QIV-015

Design overview

Safety and immunogenicity data from study FLU D-QIV-015 in older children and adults were previously reviewed and approved in November 2016 to support a change in the manufacturing process (see the Summary Basis for Regulatory Action for STN 125127/775; http://wayback.archive-it.org/7993/20170723030234/https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM531515.pdf). An annex, which included the safety and immunogenicity data from children 6 through 35 months of age, to the report was submitted to this sBLA to support the manufacturing bridging of the FLU D-QIV-004 and FLU D-QIV-009 study data (generated with the process licensed at the time the study conduct) to the new FLU D-QIV manufacturing process.

Study FLU D-QIV 015 was a phase 3 double blind, 1:1 randomized study comparing the licensed formulation of Fluarix Quadrivalent (FLU D-QIV-LP) to an investigational formulation (FLU D-QIV-IP). For subjects aged 6 through 35 months, the study was conducted in five countries (Bangladesh, France, Germany, Spain, and Poland) and enrolled consented eligible subjects that included those with chronic medical conditions predisposing to a risk of influenza complications (these subjects were excluded from Study FLU D-QIV 004) .

Primed subjects (those who had prior receipt of influenza vaccination) ages 6 through 35 months were followed for 28 days with blood draws on days 0 and 28; those who were unprimed were followed for 56 days post vaccination with had blood draws on days 0 and then day 28 before vaccination with dose 2 and again at day 56. Solicited reactions were recorded on diary card for 7 days post-vaccination. Unsolicited AEs were collected for 28 days post-vaccination and SAEs were collected throughout the study. Medically attended adverse events (MAEs) and SAEs including deaths were monitored for 180 days following vaccination.

The primary immunogenicity endpoint for subjects 6 through 35 months of age was to demonstrate non-inferiority of FLU D-QIV-IP as compared to FLU D-QIV-LP in terms of HI GMT's and GMT ratio for each of the vaccine influenza strains at 28 days after completion of the vaccination series. The next sequential primary endpoint was the occurrence of fever (≥38^{0}C) after dose 1 or dose 2 (overall per subject) during the 7 days post-vaccination period in terms of percentage and relative risk (FLU D-QIV IP/FLU D-QIV LP).

The safety assessments included solicited and general AEs for 7 days following vaccination, unsolicited AEs for 28 days following vaccination, and MAEs and SAEs for the entire study period, which was 28 or 56 days depending on the subject's vaccine-priming status.

Results

The first subject was enrolled on 18 August 2014 and the last subject completed the study on 18 April 2015, with the database freeze date of 16 July 2015. The total vaccinated cohort consisted of 940 subjects (466 in the FLU D-QIV-IP group and 474 in the FLU D-QIV-LP group). The According to Protocol cohort for analysis of immunogenicity consisted of 859 subjects (432 in the FLU D-QIV-IP group and 427 in the FLU D-QIV-LP group).

With regard to the primary immunogenicity endpoint, immunological non-inferiority of FLU D-QIV-IP to FLU D-QIV-LP was demonstrated at day 28 after completion of the vaccination series; the UL of the 95% CI of the GMT ratio D-QIV-LP/IP was ≤ 1.5 for each of the vaccine strains. The HI GMTs ranged from 32.1 to 100.8 in the FLU Q-QIV-IP group and from 38 to 105.5 in the D-QIV-LP group, depending on the vaccine strain (Table 17). The FLU D-QIV-IP group had a seroconversion rate of ≥ 49.4% and the FLU D-QIV-LP had a seroconversion rate of ≥ 49.9%.

Table 17. Study FLU D-QIV 015. Adjusted Geometric Mean Titer Ratios of Flu A/H1N1, Flu A/H3N2, Flu B/Yamagata, Flu B/Victoria HI antibodies between groups 28 days post last vaccination in subjects aged 6-35 months (ATP cohort for immunogenicity)

	D-QIV LP[1]		D-QIV IP[2]		Adjusted GMT Ratio (D-QIV LP/D-QIV IP)		
Antibody	**N[3]**	**Adjusted GMT[4]**	**N**	**Adjusted GMT**	**Value**	**LL 95% CI[5]**	**UL 95% CI[6]**
Flu A/H1N1	424	105.3	431	98	1.07	0.9	**1.28**
Flu A/H3N2	423	56.3	431	47.7	1.18	1	**1.39**
Flu B/Yamagata	423	106.4	431	99.2	1.07	0.91	**1.27**
Flu B/Victoria	423	37.7	431	32.2	1.17	0.99	**1.38**

Source: Adapted from STN 125127/775.0: Study Report Body FLU D-QIV 015, Table 84.
[1] GSK Biologicals' quadrivalent influenza vaccine produced using the licensed process
[2] GSK Biologicals' quadrivalent influenza vaccine produced using the investigational process
[3] Number of subjects with both pre- and post-vaccination results available
[4] Geometric mean antibody titer adjusted for baseline titer
[5] Lower limit of 95% confidence interval for the adjusted GMT ratio
[6] Upper limit of 95% confidence interval for the adjusted GMT ratio

With regard to the sequential primary endpoint of occurrence of fever, the relative risk of any fever (≥38°C) for FLU D-QIV-IP compared to FLU D-QIV-LP during a 7-day follow-up period was 1.06 with a 95% CI of [0.75; 1.5]. A total of 15.6% and 14.7% of subjects in the FLU D-QIV-IP and FLU D-QIV-LP groups, respectively had fever (≥38°C).

Safety results are summarized as follows:

- Solicited local AEs: Overall, injection site pain was the most frequently reported solicited local AE (14.9% and 16.4% of subjects in the FLU D-QIV-IP and FLU D-QIV-LP groups, respectively). Grade 3 injection site pain was reported for 1 subject, 0.2% and 2 subjects, or 0.4% of subjects, respectively. The incidence of the solicited local AEs did not increase after the second dose.
- Solicited general AEs: Overall, irritability/fussiness was the most frequently reported solicited general AE (26.8% and 20.4% of subjects in the FLU D-QIV-IP and FLU D-QIV-LP groups, respectively). The incidence of drowsiness and loss of appetite ranged between 16.2% and 20.3% across both treatment groups. During the same period, the incidence of grade 3 solicited general AEs did not exceed 2.2% in any of the treatment groups. The incidence of the solicited general AEs did not increase after the second dose.
- Unsolicited AEs: During the 28-day post-vaccination period, at least one unsolicited AE was reported for 52.1% and 55.3% of subjects in the FLU D-QIV-IP and FLU D-QIV-LP groups, respectively There were no imbalances in type or severity of AEs.
- MAEs: At least one unsolicited AE with a medically attended visit during the entire study period was reported for 50.4% and 53.2% of subjects in the FLU D-QIV-IP and FLU D-QIV-LP groups, respectively.
- SAEs: Seven subjects (1.5%) in the FLU D-QIV-IP and 11 subjects (2.3%) in the FLU D-QIV-LP group reported at least one SAE. All the SAEs were resolved during the study period and none of them were considered by the investigator to be causally related to vaccination.

***Reviewer Comment**: Local and general solicited reactions, unsolicited AEs, and MAEs were generally balanced between the treatment arms. There were no safety signals identified.*

Conclusions
Study FLU D-QIV 015 was a phase 3 double blind, randomized study comparing the licensed formulation of Fluarix Quadrivalent (FLU D-QIV-LP) to an investigational formulation (FLU D-QIV-IP). Specifically for subjects 6 through 35 months of age, immunological non-inferiority of FLU D-QIV IP to FLU D-QIV LP was demonstrated in terms of GMT ratio for all four strains contained in the vaccine. There was no statistically significant increase in fever (temperature ≥38ºC) reports in subjects 6 through 35 months of age with FLU D-QIV IP compared to FLU D-QIV LP after Dose 1 or Dose 2 within 7 days post-vaccination. D-QIV IP and D-QIV LP had similar reactogenicity and safety profiles. No new safety concerns were identified from the review of this study.

7. Integrated Overview of Efficacy

Not applicable. See Section 5.1 for discussion of the review strategy applied to the studies submitted to this sBLA. 7.1.1 Methods of Integration

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The integrated summary of safety and safety section of clinical study reports for supportive studies FLU D-QIV 009 and FLU D-QIV 015 were evaluated for deaths, SAEs

and pIMDs. See Sections 6.1.12.1 and Section 6.2 for safety assessment methods from studies FLU D-QIV 004 and FLU D-QIV 015, respectively. Study FLU D-QIV 009 had similar safety assessment methods to study FLU D-QIV 004, but only collected solicited local and general AEs, and unsolicted AEs following the first vaccination (study FLU D-QIV collected these after each vaccination). The duration of follow up for study FLU D-QIV 004 was 6-8 months depending on timing of enrollment, for study FLU D-QIV 009, it was 6 months, and for study FLU D-QIV, it was 28 or 56 days depending on the subject's vaccine priming status.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

See above Section 8.1

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

See discussion in Review Strategy, Section 5.1.

8.4 Safety Results

8.4.1 Deaths

There was one death (drowning) in a subject who received FLU D-QIV enrolled in Study FLU D-QIV 004, as described in Section 6.1.12.3. There were no deaths in Studies FLU D-QIV 009 or FLU D-QIV 015.

8.4.2 Nonfatal Serious Adverse Events

SAEs were generally balanced between the treatment groups in the 3 studies. In study FLU D-QIV 004, at least one SAE was reported for 3.6% and 3.3% of subjects in the FLU D-QIV and control groups, respectively. In study FLU D-QIV 009, at least one SAE was reported for 2.9% and 3.5% of subjects in the vaccine-primed and the vaccine-unprimed groups, respectively. In study FLU D-QIV 015, at least one SAE was reported for 1.5% and 2.3% of subjects in the D-QIV-IP and D-QIV-LP groups, respectively.

In study FLU D-QIV-004, a total of 44 subjects experienced a febrile convulsion over the entire study duration (21 subjects in the D-QIV group and 23 subjects in the Control group). Non-serious AEs of febrile convulsion were reported in 8 subjects in the D-QIV group and 8 subjects in the Control group. All cases (serious and non-serious) of febrile convulsion resolved. Within 28 days after vaccination, febrile convulsions were reported by 8 subjects in the D-QIV group (6 SAEs) and 7 subjects in the Control group (5 SAEs). Two subjects in the D-QIV group reported febrile convulsions with possible causal relationship to vaccination according to the Investigator as described below:

- Two days after dose 1 of FLU D-QIV, a 26 month old child developed febrile convulsions with rhinitis and red throat. The subject had history of 2 prior episodes of febrile convulsion before study enrollment associated common colds.
- Ten days after dose 1 of FLU D-QIV, a 22 month child developed febrile convulsion with upper respiratory tract infection symptoms.

Reviewer Comment: *These reports of febrile seizure 2 and 10 days following vaccination with FLU D-QIV were also both associated with symptoms of concurrent viral*

infection, however given the timing of recent vaccination, this reviewer agrees that there is possible causal relationship.

In study FLU D-QIV 009, one febrile convulsion was reported 100 days post-vaccination in the primed group and in study FLU D-QIV 015, one febrile convulsion was reported 31 days post-vaccination in the D-QIV-LP group, neither of which were considered by the study investigator or this reviewer as related to the study vaccine.

8.4.3 Study Dropouts/Discontinuations

In study FLU D-QIV 004, 1 subject who received FLU D-QIV experienced a fatal SAE (drowning) leading to premature discontinuation of the study and 3 subjects who received FLU Q-QIV experienced non-serious AEs leading to premature discontinuation of the study. These non-serious AEs included varicella, gastroenteritis, and an upper respiratory infection. In the control group, 6 subjects experienced an SAE and 10 subjects experienced a non-serious AE leading to premature discontinuation of the study.

In study FLU D-QIV 009, none of the subjects experienced an AE or SAE leading to premature discontinuation of the study.

In study FLU D-QIV 015, 3 subjects experienced non-serious AEs (eczema, bronchitis, stomatitis) leading to premature discontinuation of the study.

8.4.4 Common Adverse Events

The sample size for study, FLU D-QIV-004, was adequate for characterizing the reactogenicity profile of FLU D-QIV and is described in Section 6.1.12.2. Given that the other 2 studies had different comparators (FLU D-QIV revaccination in study FLU D-QIV 009 and FLU D-QIV LP in study FLU D-QIV 015), the integrated safety analysis focuses on rare and serious adverse events (deaths, SAEs, pIMDs).

8.4.6 Systemic Adverse Events

See above Section 8.4.4.

8.4.7 Local Reactogenicity

See above Section 8.4.4.

8.4.8 Potential Immune-Mediated Diseases

In Study FLU D-QIV 004, at least one pIMD was reported for 5 subjects in the FLU D-QIV group. There were no reports of pIMDs in the control group. See Section 6.1.12.5 above.

There were no reports of pIMD for the study period in study FLU D-QIV 009.

Information regarding pIMDs was not collected for study FLU D-QIV 015.

8.6 Safety Conclusions

Evaluation of the integrated summary of safety focused on deaths, SAEs, MAEs and pIMDs for studies FLU D-QIV 004, FLU D-QIV 009, and FLU D-QIV 015. There was one death (drowning) in a subject who received FLU D-QIV in study FLU D-QIV 004 and it was not related to the vaccine. There were no imbalances between treatment groups noted in number or nature of SAEs or MAEs, and the AE's reported are consistent with the data already contained in the package insert. There were 5 subjects with pIMDs reported in the FLU D-QIV group of study FLU D-QIV 004. Overall, the integrated summary of safety does not raise safety concerns.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

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

9.1.2 Use During Lactation

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

9.1.3 Pediatric Use and PREA Considerations

The safety, efficacy and immunogenicity data included in this sBLA will fulfill the PREA-postmarketing requirement for both Fluarix (trivalent formulation) and Fluarix Quadrivalent.

10. CONCLUSIONS

In children 6 through 35 months of age, FLU D-QIV met pre-specified criteria for vaccine efficacy when compared to non-influenza vaccine controls. No imbalances in safety were noted in the primary study FLU D-QIV 004 or in the evaluation of safety data for the supportive studies FLU D-QIV 009 and FLU D-QIV 015.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 18: Summary of Risk-Benefit Analysis for Fluarix Quadrivalent

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Influenza virus infection is a major cause of morbidity and mortality. • Children are a high-risk group for developing complications associated with influenza virus infection. • Influenza vaccination has been shown to be effective in reducing the incidence of influenza-like illness (ILI), hospitalization for influenza/pneumonia/other respiratory conditions, acute complications among high-risk patients, and mortality from all causes.	• Influenza virus infection is a potentially life-threatening disease. • Influenza virus infection is a serious condition, particularly in children who are high-risk for developing complications including death.
Unmet Medical Need	• Only Fluzone/Fluzone Quadrivalent and FluLaval/FluLaval Quadrivalent are approved for children ages 6 through 35 months. • Live attenuated influenza vaccine (FluMist) is approved for persons ages ≥ 2 to < 50 years.	• Vaccine shortages could lead to delays or lapses in annual vaccination in children. • Additional licensed products in in this age range will help meet the need for effective prevention of influenza.
Clinical Benefit	• The submitted clinical trial in children ages 6 through 35 months conducted under IND (FLU D-QIV 004) demonstrated absolute vaccine efficacy compared to non-influenza vaccine controls with regard to prevention of influenza disease caused by strains contained in the vaccine.	• Demonstration of absolute vaccine efficacy compared with non-influenza vaccine controls supports clinical effectiveness of Fluarix Quadrivalent. • Prevention of influenza illness in the children ages 6 through 35 months reduces morbidity and mortality associated with influenza infection in this population.
Risk	• The most common risks of vaccination with Fluarix Quadrivalent were local and systemic reactogenicity. Most reactions were mild and all resolved without sequelae. • No other safety signals were apparent in evaluation of the primary and 2 additional supportive safety studies.	• All the evidence indicates that the risk of vaccination with Fluarix Quadrivalent is minimal.
Risk Management	• The package insert describes in detail the common systemic and injection site reactions. Rarely observed conditions following influenza vaccination, such as Guillain-Barre Syndrome, are also cited.	• The package insert and the current pharmacovigilance plan are adequate to manage these risks.

11.2 Risk-Benefit Summary and Assessment

Data submitted to sBLA 125127/834 establish a substantial likelihood of benefit for prevention of laboratory-confirmed influenza caused by any influenza viral type/subtype included in the vaccine. The risks of vaccination with Fluarix Quadrivalent in children ages 6 through 35 months have been found to be minimal in association with a

substantial likelihood of benefit in the prevention of influenza disease caused by vaccine types/subtypes contained in the vaccine. Thus, the overall risk-benefit profile of this product is favorable in this young age group .

11.4 Recommendations on Regulatory Actions

The efficacy, immunogenicity and safety data reviewed here support the use of Fluarix Quadrivalent in persons ages 6 through 35 months. Fluarix (Trivalent) and Fluarix Quadrivalent are recommended for approval in children ages 6 through 35 months for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.

11.5 Labeling Review and Recommendations

Negotiations and CBER recommendations resulted in the following changes to the current labels for both Fluarix (trivalent) and Fluarix Quadrivalent:

- In Section 6.1, Clinical Trials Experience, CBER requested that the applicant update wording of titles for safety tables to Systemic Adverse Reactions instead of Systemic Adverse Events.
- In Section 8.1, Pediatric Use, CBER requested the applicant update this to state that safety and effectiveness of Fluarix Quadrivalent in individuals aged 6 months through 17 years have been established.
- In Section 14.1, the addition of study FLU D-QIV 004 efficacy results. In addition, as noted above in Section 6.1, the terminology “moderate to severe influenza” in the primary endpoint includes a wide range of adverse outcomes associated with influenza, and is not a universally recognized standard definition of moderate to severe influenza; it includes subjective diagnoses such as acute otitis media (AOM) and lower respiratory tract infection (LRI). Thus, the package insert included the terminology “adverse outcomes associated with influenza infection” instead of “moderate to severe influenza.”

11.6 Recommendations on Postmarketing Actions

No changes to the submitted pharmacovigilance plan for Fluarix (trivalent) or Fluarix Quadrivalent are recommended based on the information contained in this application.