Application Type	BLA Supplement
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Division / Office	DVRPA /OVRR
Committee Chair	Goutam Sen
Clinical Reviewer(s)	Susan Wollersheim
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Priority Review	No
Reviewer Name(s)	Charles Yin Kiu Cheung
Review Completion Date / Stamped Date	
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Supervisory Concurrence 2	Dale Horne, Chief, Vaccine Evaluation Branch, Division of Biostatistics
Applicant	GlaxoSmithKline Biologicals
Established Name	Influenza Virus Vaccine
(Proposed) Trade Name	Fluarix® Quadrivalent
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Influenza Virus Vaccine
Dosage Form(s) and Route(s) of Administration	Intramuscular Injection (IM).
Dosing Regimen	• 6 months to 8 years: 2 doses (0.5-mL each) at least 4 weeks apart for subjects not previously vaccinated with influenza vaccine; 1 or 2 doses (0.5-mL each) for subjects vaccinated with influenza vaccine in a previous season • 9 years and older: 1 dose (0.5-mL)
Indication(s) and Intended Population(s)	Active immunization against influenza in persons 6 months of age and older.

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Glossary

- AEs - adverse events
- AOM - acute otitis media
- CI - confidence interval
- GMTs - geometric mean titers
- HI - haemagglutination-inhibition
- ILI - influenza-like illness
- LL - lower limit
- LRI - low respiratory illness
- MAVs - medically attended visits
- MGI - mean geometric increase
- SAEs - serious adverse events
- SCR - seroconversion rates
- SPR - seroprotection rates
- VE - vaccine efficacy

1. EXECUTIVE SUMMARY

GlaxoSmithKline Biologicals' Fluarix® Quadrivalent (D-QIV) was initially approved in 2012 for the prevention of diseases caused by influenza A and B subtype viruses for use in persons aged 3 years and older. The applicant proposed to lower the minimum age indication from 3 years to 6 months of age. To support this new indication, the applicant presented the results of the pivotal efficacy study FLU-D-QIV-004, along with two additional studies FLU-D-QIV-009 and FLU-D-QIV-015.

In FLU-D-QIV-004, the success criteria of the two primary objectives were met. Over the 5 cohorts collected in 5 different periods across multiple non-US countries, vaccine efficacy was estimated to be 63.2% (97.5% CI: 51.8%, 72.3%) for the prevention of RT-PCR confirmed moderate to severe influenza disease and 49.8% (97.5% CI: 41.8%, 56.8%) for the prevention of RT-PCR confirmed influenza disease of any severity among children 6-35 months of age. The safety profile of the D-QIV group appears to be comparable to the control group. The study results appear to support the request to lower the age indication to 6 months of age. I defer to the clinical reviewer to evaluate the implications of the subgroup analysis where vaccine efficacy in the 6 to 11 month old children appears to be lower than in the overall 6 to 35 month old children.

2. CLINICAL AND REGULATORY BACKGROUND

GlaxoSmithKline Biological's (GSK) Fluarix® Quadrivalent was licensed under BLA 125127/513 on Dec 14, 2012. Currently, the vaccine is indicated for persons 3 years of age and older. Under the Pediatric Research Equity Act, the applicant performed study FLU-D-QIV-004 to evaluate the efficacy, immunogenicity, and safety of the vaccine in children 6 months through 35 months of age. In this current submission, GSK seeks to extend the indication down to children 6 months of age.

The applicant conducted pivotal efficacy study FLU-D-QIV-004, along with two additional studies FLU-D-QIV-009 and FLU-D-QIV-015, to support the extended indication.

I previously reviewed the clinical study report for FLU D-QIV-015 under BLA 125127/775, in which the investigational harmonization process was approved by CBER. In the Children 6-35 months cohort, the pre-specified success criterion for the primary immunogenicity endpoint (Upper Limit of GMT ratio ≤ 1.5) was met for each of the 4 influenza strains. The immunogenicity and safety profile of the vaccine manufactured by the investigational and existing manufacturing processes were comparable. This new process is planned to be implemented in the 2017-2018 influenza season.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

The submission quality was adequate for conducting a statistical review.

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

NA

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

5.1 Review Strategy

This BLA review focuses on study FLU D-QIV-004.

I defer to the clinical reviewer to evaluate the results of FLU D-QIV-009, which is a non-IND revaccination descriptive study conducted to comply with the EU Pediatric Investigational Plan (PIP) to evaluate the quality of immunological priming by a two-dose vaccination series administered one year earlier. The results of FLU D-QIV-009 did not appear to have been used in the proposed package insert submitted to BLA 125127/834.

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

- BLA 125127/834.0 dated 3/15/2017
    - Module 5.3.5.1 *Clinical Study Report for Study 115345 (FLU D-QIV-004 PRI)*
- BLA 125127/834.2 dated 4/21/2017
    - Module 5 Datasets to perform statistical analyses
- BLA 125127/834.4 dated 8/8/2017
    - Module 5.3.5.1 *Clinical Study Report for Study 115345 (FLU D-QIV-004-PRI) Amendment 2*

5.3 Table of Studies/Clinical Trials

Pivotal study:

- FLU D-QIV-004: Phase III, observer-blind, randomized, multi-center, multi-country, non-influenza vaccine comparator-controlled study to demonstrate the efficacy of GSK's FLU D-QIV vaccine, administered intramuscularly in children 6 to 35 months of age.

Supportive studies:

- FLU D-QIV-009 EXT 004: Phase III, open-label, multi-center, multi-country study to evaluate the immunogenicity, safety, and reactogenicity of a revaccination dose of GSK's FLU D-QIV vaccine, administered to children who previously participated in FLU D-QIV-004.
- Annex study report for FLU D-QIV-015: Phase III, double-blind, randomized, multi-center, multi-country study to assess safety and immunogenicity of GSK's FLU D-QIV vaccine manufactured with a new process, in adults 18 to 49 years old and in children 6 months to 17 years old.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 FLU D-QIV-004

Study FLU D-QIV-004 serves as the pivotal trial for supporting the extension of D-QIV to 6-months-old persons.

6.1.1 Objectives

Efficacy:

Primary objectives

To evaluate the efficacy of FLU D-QIV in the prevention of RT-PCR confirmed

1. 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 to 35 months.
    - Success criterion: the lower limit (LL) of the two-sided 97.5% confidence interval (CI) for VE is above 25%
2. 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 to 35 months.
    - Success criterion: the LL of the two-sided 97.5% CI for VE is above 15%.

Secondary objectives

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

1. lower respiratory illness (LRI) associated with RT-PCR confirmed influenza A and/or B (at any time starting 7 days before the onset of LRI and ending 7 days after end of LRI), when compared to non-influenza vaccine controls.

2. culture confirmed moderate to severe influenza A and/or B disease due to antigenically-matching influenza strains when compared to non-influenza vaccine controls.
3. culture confirmed influenza A and/or B disease of any severity due to antigenically-matching influenza strains when compared to non-influenza vaccine controls.
4. culture confirmed moderate to severe influenza A and/or B disease due to any seasonal influenza strain, when compared to non-influenza vaccine control.
5. culture confirmed influenza A and/or B disease of any severity due to any seasonal influenza strain, when compared to non-influenza vaccine controls.
6. Acute Otitis Media (AOM) associated with RT-PCR confirmed influenza A and/or B (at any time starting 7 days before the onset of LRI and ending 7 days after end of LRI), when compared to non-influenza vaccine controls.
7. RT-PCR confirmed severe influenza A and/or B disease, when compared to non-influenza vaccine controls.
    - For AOM, efficacy was demonstrated if the LL of the two-sided 95% CI for VE was above 10%. For all other secondary efficacy objectives, efficacy was demonstrated if the LL of the two-sided 95% CI for VE was above 15%.

Immunogenicity:

- To evaluate the immunogenicity of FLU D-QIV in terms of HI antibody response 28 days after completion of vaccination, in an immune sub-cohort of subjects.

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 events (MAV), serious adverse events (SAEs), and potential immune-mediated diseases during the entire study period.

6.1.2 Design Overview

Treatment allocation: Approximately 11,500 subjects were randomized 1:1 to receive either D-QIV or non-influenza vaccine control, using the "central internet randomization program ((b) (4) This program used an algorithm to minimize imbalance between the groups with minimization factor for age group (6-11, 12-23, and 24-35 months), vaccine-primed/vaccine-unprimed status, attendance to day-care center/school, history of recurrent AOM, and history of vaccination with conjugated pneumococcal vaccine. Vaccine-primed children are subjects who received at least two doses of seasonal influenza immunizations separated by 28 days or more. The study schedule of FLU-D-QIV-004 is listed in Table 1.

Table 1. Study schedule of FLU-D-QIV-004.

Day 0 Visit 1	**Day 28 Visit 2**	**Day 56 Visit 3 (for vaccine-unprimed subjects only)**	**End of safety follow-up contact (at least Month 6)**
Randomization	Safety/Reactogenicity follow up	Safety/Reactogenicity follow up	End of surveillance Safety follow up
Blood sample for immuno sub-cohort (vaccine-primed and vaccine-unprimed subjects)	Blood sample (all vaccine-primed subjects)	Blood sample (all vaccine-unprimed subjects)	Study conclusion
Vaccination Dose 1	Vaccination Dose 2 (all vaccine-unprimed subjects)		

Source: page 78 of the clinical study report of FLU D-QIV-004 submitted to BLA 125127/834.0.

Blinding: The study was observer-blind. During the data collection, the parents/ legally acceptable representatives or guardian of the vaccine recipient and those responsible for evaluation of any study endpoint were to be unaware of which vaccine was administered. Vaccine preparation and administration were to be done by authorized medical personnel who were not to participate in any of the study clinical evaluation. Serological data were not to be available during the study to any investigator or any person involved in the clinical conduct of the study. The laboratory in charge of laboratory testing was to be blinded to the treatment.

Immune sub-cohort: To assess immunogenicity, a subset of enrolled subjects was to be enrolled in the immune sub-cohort. The applicant planned to include approximately 400 subjects in the FLU D-QIV group and approximately 200 subjects in the control group from cohorts 1 and 2, approximately 75 subjects in the FLU D-QIV group and 75 subjects in the control group from cohort 3, and up to 50 subjects per participating country (half of the subjects in the FLU D-QIV group and half of the subjects in the control group) from cohorts 4 and 5. To assess (b) (4) antibody responses (exploratory endpoints), all subjects from the immune sub-cohort of cohort 3 and the subjects from the immune sub-cohort enrolled in the Dominican Republic and Thailand of cohort 4 were used.

- In cohort 1, there was an inadvertent unblinding. The immune sub-cohort was to select the first 100 enrolled subjects from the control group and the first 200 enrolled subjects from the FLU D-QIV group. However, the applicant noticed that after 100 subjects in the control group were selected, there was no longer blinding to the investigator, study staff, and the central study team. The applicant decided to eliminate all subjects that were enrolled after the last immune-sub-cohort subject in the control group from all ATP analyses.
- To prevent similar unblinding in subsequent cohorts, the protocol was amended: for cohort 2, the ratio for the enrollment in the immune sub-cohort remained 2:1, but subjects were randomized into the immune sub-cohort instead of selecting the first subjects enrolled. For subsequent cohorts, a 1:1 randomization was used for allocation of subjects in the immune sub-cohort.

Statistical comment:

- *After elimination of unblinded subjects from cohort 1, the immune-cohort 1 was left with 55 D-QIV subjects and 70 control subjects to calculate the seroconversion rate in the ATP cohort for immunogenicity (Table 62 of the clinical study report for FLU D-QIV-004). Using the TVC instead, the immune-cohort 1 had a total of 147 D-QIV subjects and 78 control subjects to calculate the seroconversion rate (Table 8.22 of the clinical study report for FLU D-QIV-004).*

6.1.3 Population

Healthy male or female subjects between and including 6 months and 35 months of age, at the time of first vaccination, eligible regardless of history of influenza vaccination in a previous season.

6.1.4 Study Treatments or Agents Mandated by the Protocol

In the FLU D-QIV group,

- vaccine-primed subjects were to receive one injection of FLU D-QIV on Day 0.
- vaccine-unprimed subjects were to receive two injections of FLU D-QIV, one each on Day 0 and on Day 28.

In the control group,

- subjects < 12 months old were to receive two injections of Prevenar 13 on Day 0 and on Day 28. In addition, one booster dose of Prevenar 13 was to be administered after study completion.
- vaccine-primed subjects ≥ 12 months were to receive one injection of Havrix on Day 0. In addition, one booster dose of Havrix was to be administered after study completion.
- vaccine-unprimed subjects ≥ 12 months old were to receive one injection of Havrix on Day 0 and one injection of a licensed varicella vaccine (Varilrix or Varivax/ ProVarivax) on Day 28. In addition, one booster dose of Havrix and one dose of the varicella vaccine* was to be administered after study completion. Vaccines were administered intramuscularly, except Varilrix which was to be injected subcutaneously.

*For countries with varicella vaccine administered as a 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.

The study enrolled 5 cohorts (Table 2). Different influenza strains were used in different vaccination periods.

Table 2. Strains included in the influenza vaccines by vaccination period

Influenza Subtype	**Cohort 1 [October 1, 2011 to February 27, 2012]**	**Cohort 2 [April 9 to July 24, 2012]**	**Cohort 3 [October 8, 2012 to February 4, 2013]**	**Cohort 4 [March 7 to July 17, 2013]**	**Cohort 5 [March 11 to July 30, 2014]**
Flu A (H1N1) HI	A/California/7/ 2009	A/California/7/ 2009	A/Christchurch/16/ 2010	A/Christchurch/16/ 2010	A/Christchurch/16/ 2010
Flu A (H3N2) HI	A/Victoria/210/ 2009	A/Victoria/210 / 2009	A/Victoria/361/ 2011	A/Victoria/361/201 1	A/Texas/50/2012
Flu B (Victoria) HI	B/Brisbane/60/ 2008	B/Brisbane/60/ 2008	B/Brisbane/60/ 2008	B/Brisbane/60/200 8	B/Brisbane/60/ 2008
Flu B (Yamagata) HI	B/Brisbane/3/2007	B/Hubei-Wujiagang/158/ 2009	B/Hubei-Wujiagang/158/ 2009	B/Hubei-Wujiagang/158/20 09	B/Massachusetts/ 2/2012

Source: Table 6 (page 95) of the clinical study report for FLU D-QIV-004 submitted to BLA 125127/834.0.
One subject in Cohort 5 received the second vaccination after this date, on September 12, 2014.

6.1.6 Sites and Centers

This study was conducted in multiple countries but not in the USA (Table 3). A total of 12,018 subjects were enrolled in the Total Vaccinated Cohort (TVC).

Table 3. Countries that participated in the study by cohort

Cohort	Countries
1	Belgium, Czech Republic, Poland, Spain, United Kingdom
2	Bangladesh, Dominican Republic, Honduras
3	Belgium, Czech Republic, Lebanon, Poland, Spain, Turkey, United Kingdom
4	Bangladesh, Dominican Republic, Honduras, Philippines, Thailand
5	Bangladesh, Dominican Republic, Honduras, India, Philippines, Thailand

Source: Table 6 (page95) of the clinical study report for FLU D-QIV-004 submitted to BLA 125127/834.0.

6.1.7 Surveillance/Monitoring

Surveillance for episodes of influenza-like illness (ILI), acute otitis media (AOM), and low respiratory illness (LRI) as consequences of influenza virus infection was to start 14 days after last vaccination for each subject and continued until the end of the influenza surveillance period. Nasal swabs were to be collected for qualifying events (ILI, AOM, or LRI), preferably within 24 hours of onset, but within 7 days after onset.

6.1.8 Endpoints and Criteria for Study Success

Primary endpoints

1. 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.

2. 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.

Secondary endpoints

Efficacy:

During the influenza surveillance period,

1. First occurrence of LRI with RT-PCR confirmed influenza A and/or B infection due to any seasonal influenza strain
2. First occurrence of culture-confirmed moderate to severe influenza A and/or B disease due to antigenically-matching influenza strains
3. First occurrence of culture-confirmed influenza A and/or B disease of any severity due to antigenically-matching influenza strains
4. First occurrence of culture-confirmed moderate to severe influenza A and/or B disease due to any seasonal influenza strain
5. First occurrence of culture-confirmed influenza A and/or B disease of any severity due to any seasonal influenza strain
6. First occurrence of AOM with RT-PCR confirmed influenza A and/or B infection due to any seasonal influenza strain
7. First occurrence of RT-PCR confirmed severe influenza A and/or B due to any seasonal influenza strain

Immunogenicity:

- Haemagglutination-inhibition (HI) antibody titers against each of four vaccine strains contained in FLU D-QIV
- Geometric Mean Titers (GMTs) of HI antibody titers at Days 0 and 28/56
- Seropositivity rates at Days 0 and 28/56
- Seroconversion rates (SCR) at Day 28/56
- Mean geometric increase (MGI) at Day 28/56
- Seroprotection rates (SPR) at Days 0 and 28/56

SCR is defined as the percentage of vaccinees that have either a pre-vaccination titer < 1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥ 1:10 and at least a four-fold increase in post-vaccination titer; MGI is defined as the geometric mean of the within-subject ratios of the post-vaccination reciprocal HI titers to the Day 0 reciprocal HI titers; SPR is defined as the percentage of vaccinees with a serum HI titer ≥ 1:40.

Safety:

- Solicited local and general AEs within 7 days (Day 0-Day 6) after each vaccination.
- Unsolicited AEs within 28 days (Day 0-Day 27) after each vaccination.
- Medically attended visits (MAVs) during the entire study period (≥ 6 months from first vaccination).
- Serious adverse events (SAEs) during the entire study period.
- Potential immune-mediated disease during the entire study period.

6.1.9 Statistical Considerations & Statistical Analysis Plan

For the two primary objectives, the two-sided alpha of 0.05 was equally divided and 0.025 was used for each objective. For the secondary efficacy objectives, the hypotheses were tested sequentially either at an alpha level of 0.025 (one-sided, or 95% CI) if both primary objectives were demonstrated, or at an alpha level of 0.0125 (one-sided, or 97.5% CI) if only one of the primary objectives was demonstrated. Otherwise, all the secondary efficacy objective evaluations were to be exploratory analyses.

In the sample size calculation, the applicant made the following assumptions: the attack rate of any influenza in the control group to be 9%, the attack rate of moderate to severe influenza in the control group to be 3.5%, and 10% of subjects will not be evaluable.

The applicant calculated that approximately 10,500 subjects would be required to assess the primary objectives. Based on the applicant's assumed true VE of 55% for prevention of RT-PCR confirmed moderate to severe influenza disease, a total of 240 cases would give 93% power to demonstrate that the LL of the two-sided 97.5% CI for VE is above 25%. Based on the applicant's assumed true VE of 35% for prevention of RT-PCR confirmed influenza disease of any severity, a total of 702 cases would give 90% power to demonstrate that the LL of the two-sided 97.5% CI for VE is above 15%.

The vaccine efficacy analyses used time-to-event methodology based on a proportional hazards model. To evaluate the proportional hazards assumption, the Scaled Schoenfeld residuals method was used. The applicant stated that the proportional hazards assumption held for treatment group and covariate "age category," but did not hold for the variable "cohort" in the primary objective evaluation. Subsequently, cohort was considered as a stratification factor in the model to estimate the hazard ratio/VE for all the efficacy evaluations.

Statistical comment:

- *A total of 90+242=332 cases of moderate to severe influenza disease were observed and a total of 344+662=1006 cases of influenza disease of any severity were observed. The study was adequately powered for assessing the two primary objectives.*

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The primary analyses and all confirmatory VE analyses used the According-to-protocol Time to event cohort (ATP-E Time to event). All descriptive efficacy tables were calculated using the ATP cohort for analysis of efficacy (ATP-E). The immunogenicity analyses were performed using the ATP cohort for analysis of immunogenicity. Because the percentage of subjects that were excluded from the ATP cohort for analysis of immunogenicity was greater than 5%, a second analysis based on the Total Vaccinated Cohort (TVC) for whom immunogenicity data were available was performed as a sensitivity analysis. The safety analysis was performed using the TVC.

The TVC included all subjects with at least one vaccine administration documented. The definitions of ATP for analysis for immunogenicity, ATP-E, ATP-E-Time to event are summarized in Table 4.

Table 4. Definition of the cohorts used for analyses.

ATP for analysis for immunogenicity	ATP-E	ATP-E-Time to event
• all evaluable subjects from the TVC • who met all eligibility criteria • who completed the scheduled vaccination. • who had received study vaccine(s) according to their random assignment. • for whom administration site of study vaccine was known. • who had not received a vaccine not specified or forbidden in the protocol. • for whom the randomization code had not been broken or for whom inadvertent unblinding had not occurred during the study • who complied with the procedures and intervals defined in the protocol. • who did not meet any of the criteria for elimination from an ATP analysis during the study. • who did not receive a product leading to exclusion from an ATP analysis • who did not present with a medical condition leading to exclusion from an ATP analysis	• all eligible subjects from the TVC: • 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. • who started their influenza surveillance period. • who had not received any non-protocol influenza vaccine during the relevant analysis interval. • who had not received any investigational or non-registered product (drug or vaccine) other than the study vaccine during the relevant analysis interval. • for whom the randomization code had not been broken or for whom inadvertent unblinding had not occurred during the study. • who did not meet any of the criteria for elimination from an ATP analysis during the study. • who did not receive a product leading to exclusion from an ATP analysis • who did not present with a medical condition leading to exclusion from an ATP analysis	• 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. • who started their influenza surveillance period. • Subjects with any of the following events were censored at the time of the occurrence of the event and were not eliminated: - who met any of the criteria for elimination from an ATP analysis during the study. - who received a product leading to exclusion from an ATP analysis - who presented with a medical condition leading to exclusion from an ATP analysis - who received any non-protocol influenza vaccine during the relevant analysis interval. - who received any investigational or non-registered product (drug or vaccine) other than the study vaccine during the relevant analysis interval. - for whom the randomization code had been broken or for whom inadvertent unblinding had occurred

Source: Section 5.12.5.1 (pp. 125-127) of the clinical study report for FLU-D-QIV-004.
Note: a subject who did not have a swab collected during the allowed window (0-7 days) of episode onset was not eliminated, but for all vaccine efficacy endpoints related to influenza confirmed cases, only the episode for which a swab was collected during the allowed window (0-7 days) of episode onset was considered. This is applicable for both ATP and TVC efficacy analysis.

6.1.10.1.1 Demographics

The summary statistics for demographic variables were comparable between the D-QIV and control groups in the ATP efficacy - Time to event cohort, ATP cohort for efficacy, TVC, and ATP cohort for immunogenicity, and immune subset for (b) (4) testing cohorts (Table 5 below and Tables 27 - 31 of the study report).

Table 5. Summary of demographic characteristics (ATP cohort for efficacy - Time to event)

		D-QIV N = 5707		Control N = 5697		Total N = 11404	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (months) at dose 1 vaccination	Mean	21.9	-	21.8	-	21.9	-
	SD	8.0	-	8.0	-	8.0	-
	Median	22.0	-	22.0	-	22.0	-
	Minimum	6	-	6	-	6	-
	Maximum	35	-	35	-	35	-
Gender	Female	2798	49.0	2771	48.6	5569	48.8
	Male	2909	51.0	2926	51.4	5835	51.2
Geographic Ancestry	African Heritage / African American	20	0.4	19	0.3	39	0.3
	American Indian or Alaskan Native	0	0.0	0	0.0	0	0.0
	Asian - Central/South Asian Heritage	1045	18.3	1035	18.2	2080	18.2
	Asian - East Asian Heritage	2	0.0	0	0.0	2	0.0
	Asian - Japanese Heritage	2	0.0	0	0.0	2	0.0
	Asian - South East Asian Heritage	1621	28.4	1612	28.3	3233	28.3
	Native Hawaiian or Other Pacific Islander	3	0.1	0	0.0	3	0.0
	White - Arabic / North African Heritage	130	2.3	139	2.4	269	2.4
	White - Caucasian / European Heritage	1335	23.4	1349	23.7	2684	23.5
	Other	1549	27.1	1543	27.1	3092	27.1

N = total number of subjects, n/% = number / percentage of subjects in a given category, Value = value of the considered parameter, SD = standard deviation
Source: Table 29 of the clinical study report for FLU D-QIV-004 submitted to BLA 125127/834.0.

Statistical comment:

- *The D-QIV and control groups were comparable with respect to these demographic characteristics.*

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
NA

6.1.10.1.3 Subject Disposition
The subject disposition is summarized in Table 6. Non-compliance with vaccination schedule and subjects not having received the vaccination as scheduled accounted for 90% of the subjects eliminated from the ATP cohort for efficacy-Time to event.

Table 6. Number of subjects enrolled into the study and number excluded from ATP analyses for efficacy - Time to event with reasons for exclusion

	Total (n)	**FLU D-QIV (n)**	**Control (n)**	**NOGRP (n)**
Total cohort	12046	6022	6022	2
Subjects excluded from all stat analysis	21	11	10	0
Total effective cohort	12025	6011	6012	2
Study vaccine dose not administrated but subject number allocated	7	5	0	2
Total vaccinated cohort	12018	6006	6012	0
Randomization failure	10	5	5	0
Study vaccine dose not administered according to protocol	4	1	3	0
Vaccine temperature deviation (code 1080)	24	11	13	0
Protocol violation (inclusion/exclusion criteria)	14	5	9	0
Non-compliance with vaccination schedule (including wrong and unknown dates)	243	126	117	0
Subjects who did not receive the vaccination as per their schedule	312	147	165	0
Subjects drop-out from the study before the start of the surveillance period	7	4	3	0
ATP cohort for efficacy - Time to event	11404	5707	5697	0

Source page 156 Table 25 of the clinical study report for FLU D-QIV-004 submitted to BLA 125127/834.0.
NOGRP = No assigned group; n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number; % = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary objectives of the clinical study were met (Table 7).

Table 7. Statistical analyses of primary efficacy endpoints

Event type	Result	Remark
RT-PCR confirmed moderate to severe influenza A and/or B disease due to any seasonal strain	VE 63.2% (97.5% CI: 51.8%, 72.3%)	LL > 25% Pre-specified success criterion was met.
RT-PCR confirmed influenza A and/or B disease of any severity due to any seasonal strain	VE 49.8% (97.5% CI: 41.8%, 56.8%)	LL > 15% Pre-specified success criterion was met.

Source: pages 10-11 of the clinical study report of FLU D-QIV-004 submitted to BLA 125127/834.0.

Statistical comments:

- *The lower limits were well above the success criteria.*
- *The reviewer verified these results.*

6.1.11.2 Analyses of Secondary Endpoints

Efficacy:

The pre-specified success criteria of the studies were met for all except the last endpoint (Table 8).

Table 8. Statistical analyses of secondary efficacy endpoints

Event type	Result	Remark
LRI associated with RT-PCR confirmed influenza A and/or B	VE: 54% (95% CI: 28.9%, 71.0%)	LL > 15% Pre-specified success criterion was met.
Culture confirmed moderate to severe influenza A and/or B disease due to antigenically-matching influenza strains	VE: 77.6% (95% CI: 64.3%, 86.6%)	LL > 15% Pre-specified success criterion was met.
Culture confirmed influenza A and/or B of any severity due to antigenically-matching influenza strains	VE 60.1% (95% CI: 49.1%, 69.0%)	LL > 15% Pre-specified success criterion was met.
Culture confirmed moderate to severe influenza A and/or B disease due to any seasonal influenza strains	VE: 63.8% (95% CI: 53.4%, 72.2%)	LL > 15% Pre-specified success criterion was met.
Culture confirmed influenza A and/or B disease of any severity due to any seasonal influenza strains	VE: 51.2% (95% CI: 44.1%, 57.6%)	LL > 15% Pre-specified success criterion was met.
Acute otitis media (AOM) associated with RT-PCR confirmed influenza A and/or B disease	VE: 56.6% (95% CI: 16.7%, 78.8%)	LL > 10% Pre-specified success criterion was met.
RT-PCR confirmed severe influenza A and/or B disease	VE: 34.2% (95% CI: -297.3%, 91.3%)	LL > 15% Pre-specified success criterion was not met.

Source: pages 10-12 of the clinical study report of FLU D-QIV-004 submitted to BLA 125127/834.0.

Reviewer's comment:

- *The study had very few cases of RT-PCR confirmed severe influenza A and/or B disease (2 cases in D-QIV group and 3 cases in the control group). Hence, there was an insufficient sample size to evaluate the objective that D-QIV prevents RT-PCR confirmed severe influenza A and/or B disease.*

Immunogenicity:

The HI immune responses of subjects pre- and post-vaccination were tabulated (Table 9).

Table 9. Summary of HI immune response at pre and post vaccination.

			N	≥10		SPR		GMT	N'	SCR		MGI
Antibody	**Group**	**Timin**		**n''**	**%**	**n**	**%**	**Value**		**n'**	**%**	**Value**
Flu A (H1N1) HI	D-QIV	PRE	744	200	26.9	182	24.5	11.9	-	-		
		POST	752	728	96.8	640	85.1	165.3	743	596	80.2	14.0
	Control	PRE	567	152	26.8	134	23.6	11.9	-	-		
		POST	578	170	29.4	146	25.3	12.6	566	20	3.5	1.1
Flu A (H3N2) HI	D-QIV	PRE	746	266	35.7	238	31.9	14.8	-	-		
		POST	753	740	98.3	612	81.3	132.1	746	513	68.8	9.0
	Control	PRE	568	187	32.9	159	28.0	13.4	-	-		
		POST	578	210	36.3	175	30.3	14.7	567	24	4.2	1.1
Flu B (Victoria) HI	D-QIV	PRE	745	205	27.5	143	19.2	10.0	-	-		
		POST	750	701	93.5	539	71.9	92.6	742	514	69.3	9.3
	Control	PRE	567	138	24.3	103	18.2	9.2	-	-		
		POST	579	147	25.4	101	17.4	9.2	567	5	0.9	1.0
Flu B (Yamagata) HI	D-QIV	PRE	745	134	18.0	73	9.8	7.3	-	-		
		POST	753	719	95.5	638	84.7	121.4	745	605	81.2	16.7
	Control	PRE	568	93	16.4	59	10.4	7.3	-	-		
		POST	579	108	18.7	64	11.1	7.6	568	13	2.3	1.1

Source: Table 61 (page 222) of the clinical study report of FLU D-QIV-004 submitted to BLA 125127/834.0.
MGI=geometric mean of the within-subject ratios of the post-vaccination reciprocal HI titer to the Day 0 reciprocal HI titer
N =Number of subjects with results available (for seropositivity rates, SPR and GMT computation)
N'=Number of subjects with both pre and post results available (for SCR and MGI computation)
n''/%= number/percentage of subjects with titer equal to or above specified value
n/% = Number/percentage of seroprotected subjects
n'/% = Number/percentage of seroconverted subjects

Reviewer's comment:

- *The post-vaccination seropositivity rate and seroconversion rate for each antigen in the D-QIV group was at least 71.9% and 68.8%, respectively. The summary statistics comparing the D-QIV and control groups and comparing pre- and post-vaccination in the D-QIV group suggest that the D-QIV vaccine elicited immune response.*

6.1.11.3 Subpopulation Analyses

Age subgroups

Descriptively, the point estimates of vaccine efficacy for RT-PCR confirmed moderate to severe influenza and for RT-PCR confirmed influenza of any severity (primary objectives) appear to be higher in the 18-35 months subgroup than in the 6-17 months subgroup (Tables 7.7 and 7.8 of the clinical study report for FLU D-QIV-004). In addition, the point estimates of vaccine efficacy for the majority of event types assessed in the secondary objectives also showed similar pattern between the age subgroups (Table 7.9 of the clinical study report for FLU D-QIV-004).

Among subjects between 6 and 11 months of age, vaccine efficacy for the RT-PCR confirmed influenza of any severity was 19.2% (95% CI: -29.3%, 49.9%) (Table 7.5 of the clinical study report for FLU-QIV-004). The point estimate is lower than those for subjects between 6 and 17 months of age (43.3% (95% CI: 27.8%, 55.8%)) and between 18 and 35 months of age (51.6% (95% CI: 43.7%, 58.4%)) (Table 7.8 of the clinical study report for FLU-QIV-004).

Statistical comment:

- *Despite the low vaccine efficacy estimated for RT-PCR confirmed influenza of any severity among subjects 6 to 11 months of age, the vaccine still appears to elicit immune response in this age group (Table 8.18 of the clinical study report for FLU-QIV-004). I defer to the clinical reviewer to interpret the clinical relevance of these results.*

Countries

For most countries, the point estimates of vaccine efficacy for the primary objectives appear to be at least modest (> 30%), with the exception of Turkey (no cases to estimate) and Thailand (Tables 7.10 – 7.11 of the clinical study report for FLU-QIV-004). However, the wide confidence intervals suggest that these estimates are not reliable.

Cohorts

A total of 5 cohorts were used in this study. These cohorts reflected subgroups performed at different vaccination periods (Table 2). Vaccine efficacy estimates for the primary objectives appear to vary somewhat among cohorts, but the estimates appear to be at least modest (>30%) in each cohort (Tables 7.13 and 7.14 of the clinical study report for FLU-QIV-004).

6.1.11.4 Dropouts and/or Discontinuations

The numbers of subjects withdrawn from the study due to various causes were comparable between the D-QIV and control groups (Table 10).

Table 10. 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	5808	5804	11612
Number of subjects withdrawn	198	208	406
Reasons for withdrawal :			
-Serious Adverse Event	1	6	7
-Non-Serious Adverse Event	3	10	13
-Protocol violation	1	0	1
-Consent withdrawal (not due to an adverse event)	140	129	269
-Migrated/moved from study area	20	23	43
-Lost to follow-up (subjects with incomplete vaccination course)	6	16	22
-Lost to follow-up (subjects with complete vaccination course)	17	19	36
-Sponsor study termination	0	0	0
-Others	10	5	15

Source: page 156 Table 23 of the clinical study report of FLU D-QIV-004 submitted to BLA 125127/834.0

6.1.11.5 Exploratory and Post Hoc Analyses

These analyses were not considered in this statistical review.

6.1.12 Safety Analyses

Table 11 summarizes the rates of solicited local and systemic adverse events by types for the D-QIV and control groups. Table 12 provides an overview of the rates and numbers of unsolicited adverse events for the D-QIV and control groups. Among unsolicited AEs, nasopharyngitis (14.5% and 15.7% of subjects in the Flu D-QIV and control groups, respectively) and upper respiratory tract infection (8.7% and 8.6% of subjects in the FLU D-QIV and control groups, respectively) were the most frequently reported. Table 13 provides an overview of the rates and numbers of medically attended events for the D-QIV and control groups.

Table 11: Percentage of subjects experiencing solicited local and systemic adverse events after two doses of vaccination.

	Any		**Grade 3**	
	D-QIV	**Control**	**D-QIV**	**Control**
Local	**% (N=5907)**	**% (N=5901)**	**% (N=5907)**	**% (N=5901)**
Pain	22.9	23.3	0.7	0.8
Redness	16.6	18.5	0.1	0.0
Swelling	11.3	12.6	0.0	0.1
Systemic	**% (N=5908)**	**% (N=5901)**	**% (N=5908)**	**% (N=5901)**
Drowsiness	17.3	19.1	1.0	1.2
Irritability/ fussiness	23.4	24.2	1.3	1.8
Loss of appetite	20.8	21.8	1.9	1.6
Temperature/ (Axillary) (°C)	11.6	12.8	2.3	2.4

Source: Tables 74 and 75 of the clinical study report for FLU D-QIV-004 submitted to BLA 125127/834
Definition of Grade 3 fever: > 39.0°C; Grade 3 redness/swelling: >50mm

Table 12. Unsolicited adverse events in FLU-D-QIV-004

	Group		
	D-QIV N=6006	**Control N=6012**	**Total N=12018**
Unsolicited adverse events	2640 (44.0%)	2679 (44.6%)	5319 (44.3%)
Grade 3 Unsolicited adverse events	160 (2.7%)	149 (2.5%)	309 (2.6%)
Unsolicited adverse events with causal relationship to vaccination	106 (1.8%)	116 (1.9%)	222 (1.8%)
Grade 3 Unsolicited adverse events with causal relationship to vaccination	7 (0.1%)	3 (0.0%)	10 (0.1%)

Source: Table 9.33 page 1560 of the clinical study report for FLU D-QIV-004 submitted to BLA 125127/834

Table 13. Medically attended events in FLU-D-QIV-004

	Group		
	D-QIV N=6006	**Control N=6012**	**Total N=12018**
Unsolicited adverse events with medically attended events	3885 (64.7%)	3988 (66.3%)	7873 (65.5%)
Grade 3 Unsolicited adverse events with medically attended events	200 (3.3%)	211 (3.5%)	411 (3.4%)
Unsolicited adverse events with causal relationship to vaccination with medically attended events	57 (0.9%)	58 (1.0%)	115 (1.0%)
Grade 3 Unsolicited adverse events with causal relationship to vaccination with medically attended events	4 (0.1%)	2 (0.0%)	6 (0.0%)

Source: Table 9.35 of the clinical study report for FLU D-QIV-004 submitted to BLA 125127/834

Reviewer's comment:

- *The percentages of subjects experiencing each type of solicited adverse event appear to be comparable between the D-QIV and control groups. In addition, the aggregated rates of unsolicited adverse events and medically attended events also appear to be comparable between the D-QIV and control groups.*

6.1.12.1 Methods

Safety was evaluated using the TVC. Adverse events were summarized descriptively. The percentages of subjects with specific adverse events were summarized with their exact 95% CIs.

6.1.12.3 Deaths

Four subjects experienced a total of 6 SAEs associated with a fatal outcome. One subject was in the FLU D-QIV group and the other 3 were in the control group. None of the SAEs with fatal outcome were attributed to the study vaccine.

- In the FLU D-QIV, a 20-months old male child died due to drowning (b) (6) days after receiving the first dose of FLU D-QIV.
- In the control group, two subjects died due to drowning. One subject in the control group died from complications of bronchitis, pneumonia, and pleural effusion (b) (6) days after the second dose of control vaccine.

6.1.12.4 Nonfatal Serious Adverse Events

In the D-QIV group, 217 out of 6006 subjects reported at least one unsolicited SAE (3.6%). Of those subjects, 6 were identified to have SAE caused by vaccination: immune thrombocytopenic purpura, hypersensitivity, nephrotic syndrome, apnoea, and 2 facial paralysis febrile convulsion cases. In the control group, 201 out of 6012 subjects reported at least one unsolicited SAE (3.3%). Of those subjects, 2 were identified to have SAE caused by vaccination (febrile convulsion and seizure anoxic).

Statistical comment:

- *There did not appear to be major imbalance in the occurrence of SAEs by event types between the D-QIV and control groups (Table 9.29 of the clinical study report for FLU D-QIV-004).*

6.1.12.5 Adverse Events of Special Interest (AESI)

Potential immune-mediated diseases that included autoimmune diseases and other inflammatory and/or neurologic disorders were of special interest. A total of 4 subjects experienced one pIMD (immune thrombocytopenic purpura, coeliac disease, facial paralysis (2)), and 1 subject experienced 3 pIMDs (nephrotic syndrome, anaphylactic shock, and venous thrombosis).

Statistical comment:
- *I defer to the clinical reviewer to evaluate these results.*

6.1.12.6 Clinical Test Results

NA

6.1.12.7 Dropouts and/or Discontinuations

Please refer to Table 10 in Section 6.1.11.4 of this review. The number of dropouts due to serious adverse events and non-serious adverse events were slightly higher in the control group than in the D-QIV group. However, the counts were small. The total number of subjects that withdrew from the study appears to be similar between the D-QIV group and control group. The dropouts do not appear to present an issue in this clinical study.

7. Integrated Overview of Efficacy

N/A

8. Integrated Overview of Safety

N/A

9. Additional Statistical Issues

NA

10. Conclusions

10.1 Statistical Issues and Collective Evidence

Efficacy:

The success criteria of the two primary objectives were met. Vaccine efficacy for RT-PCR confirmed moderate to severe influenza A and/or B disease due to any seasonal strain was estimated to be 63.2% (97.5% CI: 51.8%, 72.3%). Vaccine efficacy for RT-PCR confirmed influenza A and/or B disease of any severity due to any seasonal strain was estimated to be 49.8% (97.5% CI: 41.8%, 56.8%). In addition, the success criteria of 6 of the 7 secondary objectives were met. With only a total of 2 cases in the D-QIV group

and 3 cases in the control group, there was inadequate power to demonstrate that D-QIV is efficacious in the prevention of RT-PCR confirmed severe influenza A and/or B disease.

In a subgroup analysis assessing the 6 to 11 month old subjects, vaccine efficacy for RT-PCR confirmed influenza of any severity was estimated to be 19.2%, with a wide 95% confidence interval of (-29.3%, 49.9%). This point estimate was considerably lower than the overall VE among children between 6 and 35 months of age (49.8%).

Safety:
The safety profile of the D-QIV group and the control group appears to be comparable.

10.2 Conclusions and Recommendations

The results of study FLU D-QIV-004 suggest that the safety profile is comparable between the D-QIV and control groups, and D-QIV is efficacious overall among children 6 to 35 months of age. I defer to the clinical reviewer to evaluate the clinical significance of the lower estimated vaccine efficacy in the subgroup of 6 to 11 month old children.