Statistical Review and Evaluation	
Application Type	Efficacy (Immunogenicity) Supplement
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Applicant	GlaxoSmithKline Biologicals
Established Name	(Quadrivalent Inactivated Split Virion) Influenza Vaccine
Trade Name	FluLaval® Quadrivalent
Pharmacologic Class	Vaccine
Formulation	0.5 mL/dose contains 15 µg haemaglutinin for each of the A/H1N1, A/H3N2, B/Yamagata and B/Victoria strains
Dosage Form(s) and Route(s) of Administration	Intramuscular administration of 0.5 mL/dose
Dosing Regimen	For subjects 6 to 35 months of age: 1 dose for vaccine-primed subjects and 2 doses (Day 0 and Day 28) for vaccine-unprimed subjects
Indication(s) and Intended Population(s)	Active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine

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1. Executive Summary

This submission includes the applicant's clinical study report (CSR) of a Phase 3 trial (FLU Q-QIV-022) for fulfilment of a post-marketing requirement. The applicant is seeking an indication for use of FluLaval Quadrivalent in children 6 to 35 months of age, based on FLU Q-QIV-022 and the 3 supportive clinical studies FLU Q-QIV-021, FLU Q-QIV-013, and FLU Q-QIV-003. This review will focus on FLU Q-QIV-022.

FLU Q-QIV-022 was a Phase 3, observer-blind, randomized, controlled, multi-center (67 centers in US and 2 centers in Mexico) study to evaluate the immunogenicity and safety of GSK Biologicals' quadrivalent influenza vaccine candidate (Q-QIV), compared to Sanofi Pasteur's quadrivalent influenza vaccine, Fluzone® Quadrivalent (F-QIV), administered intramuscularly to children 6 to 35 months of age. Vaccine-primed subjects were to receive only 1 dose (Day 0), and vaccine-unprimed subjects were to receive 2 doses (Day 0 and Day 28). The FLU Q-QIV vaccine contained 15µg Haemaglutinin (HA) of each of the A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains (total injected volume was 0.50 mL/dose), while Fluzone Quadrivalent (F-QIV) contained 7.5 µg of each of the same strains (total injected volume was 0.25 mL/dose).

A total of 2424 subjects were vaccinated (1207 in the FLU Q-QIV Group, and 1217 in the F-QIV Group; Total Vaccinated Cohort (TVC)). The According-To-Protocol (ATP) Cohort for immunogenicity included 972 subjects in the Q-QIV Group, and 980 in the F-QIV Group for A/H1N1 and A/H3N2 (see Section 6.1.2 for further details on number of subjects in the ATP cohort for each of the B strains). The primary immunogenicity objective was to demonstrate immunogenic non-inferiority of Q-QIV to F-QIV, in terms of geometric mean titers (GMTs) and seroconversion rates (SCRs) 28 days after completion of dosing.

In the ATP Cohort for immunogenicity, non-inferior immunogenicity of Q-QIV compared to F-QIV was shown based on the pre-specified non-inferiority criteria [the upper limit of the 2-sided 95% CI for the GMT ratio (F-QIV/Q-QIV) of < 1.5, and the upper limit of the 2-sided 95% CI for the difference in SCRs (F-QIV – Q-QIV) of <10%, for each of the 4 strains].

In the TVC, a total of 56 SAEs were reported for 43 subjects during the entire study period; 29 SAEs were reported for 22 subjects (1.8%) in the Q-QIV group, and 28 SAEs were reported for 21 subjects (1.7%) in the F-QIV group. All SAEs in the Q-QIV group were reported as resolved, with the exception of one case of Kawasaki's disease and one case of croup. All SAEs in the F-QIV group were also reported as resolved at the time of this report, with the exception of 4 SAEs (B precursor type acute leukemia, failure to thrive, developmental delay, and hemiplegia) reported in 3 subjects. No fatal events were reported during the entire study period.

The incidence of any fever (≥38C; overall/dose) during the 7-day post-vaccination period in the Q-QIV group and the F-QIV group was 5.8% and 5.4%, respectively. It should be noted that the reviewer found that ~2% of the fever observations are ≤35C, which the

applicant claimed to be “mishandling by the parents.” However, no significant difference in the distribution of fever between the two groups was observed.

2. Clinical and Regulatory Background

Please refer to this section in the medical officer’s review.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

This submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices and Data Integrity

No data integrity issues with respect to efficacy (immunogenicity) were found. However, ~2% of the fever observations are ≤35C, which the applicant claimed was “mishandling by the parents.” It is not verifiable whether this “mishandling by the parents” was restricted to fever observations ≤35C.

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

5.1 Review Strategy

This submission includes the clinical study report of FLU Q-QIV-022. Statistical aspects of the immunogenicity and safety analyses were reviewed.

5.2 BLA Documents that Serve as the Basis for the Statistical Review

This submission (STN 125163/405) was received on 1/27/2016, and is located in the EDR. The Clinical Study Reports (CSR), electronic datasets, and Case Report Forms (CRF) for FLU Q-QIV-022 are located in section 5.3.5.1 of this submission.

6. Discussion of Individual Studies/Clinical Trials

6.1 Clinical Trial #1: FLU Q-QIV-022

Title of the clinical trial: "A Phase 3, observer-blind, randomized, controlled, multi-center study to evaluate the immunogenicity and safety of GSK Biologicals' quadrivalent influenza vaccine candidate, GSK2282512A (Q-QIV), compared to Sanofi Pasteur's quadrivalent influenza vaccine Fluzone® Quadrivalent, administered intramuscularly to children 6 to 35 months of age."

Date of study initiation: 10/1/2014
Date of study completion: 6/23/2015

6.1.1 Objective(s)

The primary immunogenicity objective was to demonstrate the immunogenic non-inferiority of GSK Biologicals' quadrivalent influenza vaccine candidate (Q-QIV) to Fluzone Quadrivalent (F-QIV), in terms of geometric mean titers (GMTs) and seroconversion rates (SCRs), 28 days after completion of dosing (Day 28 and Day 56 for vaccine-primed and vaccine-unprimed subjects, respectively). The clinical efficacy of the vaccine was not evaluated in this study.

6.1.2 Design Overview

FLU Q-QIV-022 was a Phase 3, observer-blind, randomized, controlled, multi-country (US and Mexico), multi-center (69 centers; 67 in US and 2 in Mexico) clinical trial with parallel treatment groups (Q-QIV vs. F-QIV). Duration of the study was approximately 6 months for each enrolled subject to complete the study.

Subjects 6-35 months of age were randomized to receive either Q-QIV or F-QIV in a 1:1 ratio. Age (6-17 and 18-35 months), study center, and the pre-study influenza vaccination status of the subjects were minimization factors to ensure balanced representation of the combination of minimization factors in the two study groups. The study aimed to enroll at least 40% but no more than 50% of the total subjects in the group 6-17 months of age.

Vaccination schedule was

(i) Vaccine-primed subjects: one intramuscular (IM) injection, on Day 0.
(ii) Vaccine-unprimed subjects: two IM injections, on Days 0 and 28.

A total of 2424 subjects were vaccinated (1207 in the FLU Q-QIV Group, and 1217 in the F-QIV Group; Total Vaccinated Cohort (TVC)). Of these, 41.3% (1002 subjects in TVC cohort) were 6-17 months of age. The According-To-Protocol (ATP) Cohort for immunogenicity included 972 subjects in the Q-QIV Group and 980 in the F-QIV Group for A/H1N1 and A/H3N2. The According-To-Protocol (ATP) Cohort for immunogenicity included 974 subjects in the Q-QIV Group and 980 in the F-QIV Group for B/Yamagata. The According-To-Protocol (ATP) Cohort for immunogenicity included 973 subjects in the Q-QIV Group and 980 in the F-QIV Group for B/Victoria.

In the TVC, 46.6% (1129/2424) were female; 64.4% were white, 15.6% black, and 20.0% other (Asian, Pacific Islander, Native American, and mixed).

6.1.3 Population

The key inclusion criteria for the enrollment of this trial were:

- Subject's parent(s)/Legally Acceptable Representative(s) [LAR(s)] who, in the opinion of the investigator, could and would comply with the requirements of the protocol (e.g., completion of diary cards, return for follow-up visits)
- A male or female between, and including, 6 and 35 months of age at the time of the first vaccination
- Written informed consent obtained from the parent(s)/LAR(s) of the subject
- Subject in stable health as determined by the investigator's clinical examination and assessment of the subject's medical history

6.1.4 Study Treatments or Agents Mandated by the Protocol

Study vaccine (Q-QIV):
Q-QIV contained 15μg Haemaglutinin (HA) of each of the A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains (total injected volume was 0.50 mL/dose).

Comparator vaccine (F-QIV):
F-QIVcontained 7.5 μg of each of the same strains (total injected volume was 0.25 mL/dose).

Q-QIV or F-QIV was administered intramuscularly in the deltoid region of the non-dominant arm (subjects ≥ 12 months of age) or anterolateral thigh region (subjects <12 months of age). Vaccine-primed subjects were to receive only 1 dose (Day 0), and vaccine-unprimed subjects were to receive 2 doses (Day 0 and Day 28).

6.1.6 Sites and centers

This study was conducted in 69 centers in the US and Mexico. Sixty-seven centers were in the US.

6.1.7 Surveillance/Monitoring

Please refer to this section in the medical officer's review.

6.1.8 Endpoints and Criteria for Study Success

Primary immunogenicity endpoints:
The primary immunogenicity endpoint was humoral immune response to each strain. Serum HI antibody titers for each of the four strains 28 days after the last vaccine dose was used to calculate

(i) GMT ratio (F-QIV/Q-QIV)

(ii) SCR difference (F-QIV - Q-QIV).

Criteria for study success:

(i) The upper limit of the 2-sided 95% CI for the GMT ratio (F-QIV/Q-QIV) < 1.5 for each of the 4 strains

(ii) The upper limit of the 2-sided 95% CI for the difference in SCRs (F-QIV - Q-QIV) <10% for each of the 4 strains.

6.1.9 Statistical Considerations and Statistical Analysis Plan

The GMT ratio and difference in SCRs between groups were calculated to assess the immunogenic non-inferiority of Q-QIV to F-QIV:

(i) The GMT ratio (adjusted for baseline titer) of F-QIV over Q-QIV and the two-sided 95% CI for each of the 4 strains was calculated

(ii) The difference in SCRs (F-QIV minus Q-QIV) and the two-sided 95% CI for each of the 4 strains was calculated.

6.1.11 Immunogenicity Analyses

6.1.11.1 Analyses of Primary Immunogenicity Endpoint

The analysis of the primary immunogenicity endpoint was performed on the ATP Cohort for immunogenicity, as described in section 6.1.2.

The following Tables 1 and 2 show the primary immunogenicity results that the applicant proposed to present in the PI.

Table 1: GMT ratios (F-QIV/Q-QIV), adjusted for baseline titer, at 28 days after the last vaccine dose

	F-QIV		Q-QIV		
Strain	n	GMT	n	GMT	GMT ratio (95% CI)
H1N1	980	85.1	972	99.6	0.85 (0.77, **0.95**)
H3N2	980	84.6	972	99.8	0.85 (0.77, **0.94**)
B/Yamagata	980	167.3	974	258.1	0.65 (0.59, **0.71**)
B/Victoria	980	33.7	973	54.5	0.62 (0.56, **0.69**)

Source: Extracted from Table 22 in the applicant's CSR (page 82). The numerical accuracy was verified by the reviewer.

Table 2: Difference in SCRs (F-QIV - Q-QIV) at 28 days after the last vaccine dose

	F-QIV	Q-QIV	Difference in SCRs
Strain	SCR	SCR	(95% CI)
H1N1	67.3%	73.7%	-6.3 (-10.3, **-2.3**)
H3N2	69.4%	76.1%	-6.7 (-10.7, **-2.8**)
B/Yamagata	73.8%	85.5%	-11.8 (-15.3, **-8.2**)
B/Victoria	48.5%	64.9%	-16.4 (-20.7, **-12.0**)

Source: Extracted from Table 23 in the applicant's CSR (page 82). The numerical accuracy was verified by the reviewer.

Reviewer's Comments:

1. Immunogenicity results on TVC are similar to the immunogenicity results on the ATP Cohort for immunogenicity.
2. Among the subjects in this study (6-35 months of age), Q-QIV appears to be immunogenically non-inferior to F-QIV in terms of GMT ratio and SCR difference for all four strains contained in the vaccine, as shown in Tables 1 and 2 (for success criteria, please see section 6.1.8).

6.1.12 Safety Analyses

In the Total Vaccinated Cohort (TVC), 56 SAEs were reported for 43 subjects during the entire study period; 29 SAEs were reported for 22 subjects (1.8%) in the Q-QIV group, and 28 SAEs were reported for 21 subjects (1.7%) in the F-QIV group. All SAEs in the Q-QIV group were reported as resolved, with the exception of one case of Kawasaki's disease (age at onset: 17 months) and one case of croup (age at onset: 19 months). All SAEs in the F-QIV group were also reported as resolved at the time of this report, except for 4 SAEs (B precursor type acute leukemia, failure to thrive, developmental delay, and hemiplegia) reported in 3 subjects. (Developmental delay and hemiplegia occurred in the same subject; age at onset was 36 months.) No fatal events were reported during the entire study period.

The incidence of any fever (≥38C; overall/dose) during the 7-day post-vaccination period in the Q-QIV group and the F-QIV group was 5.8% and 5.4%, respectively.

Reviewer's Comments:

1. The reviewer found that ~2% of the fever observations are ≤35C, which the applicant claimed to be "mishandling by the parents."
2. However, no significant difference in the distribution of fever between the two groups was observed.
3. Whether this "mishandling by the parents" was restricted to fever observations ≤35C or was a systematic problem across all fever observations is not verifiable.

6.1.13 Subgroup Analyses

The subgroup analyses of immunogenicity and safety by age, sex, ethnicity, and country generally were shown to be consistent with the overall immunogenicity and safety results.

The subgroup analyses of immunogenicity by age and sex are shown in Tables 3-6. Subgroup analysis of immunogenicity by ethnicity is not shown because the majority (~80%) of the subjects were either white or black. Moreover, there was no difference observed between white and black subjects in terms of immunogenicity. Subgroup analysis of immunogenicity by country was not shown because the majority (>90%) of subjects were from the US.

Table 3: GMT ratios (F-QIV/Q-QIV), adjusted for baseline titer, at 28 days after the last vaccine dose, by age

Strain	**6-23 months** GMT ratio (95% CI)	**24-35 months** GMT ratio (95% CI)
H1N1	0.85 (0.75, 0.98)	0.83 (0.70, 0.98)
H3N2	0.82 (0.72, 0.93)	0.88 (0.75, 1.03)
B/Yamagata	0.55 (0.49, 0.61)	0.80 (0.70, 0.92)
B/Victoria	0.53 (0.47, 0.61)	0.77 (0.66, 0.91)

Source: Extracted from Table 14 in the applicant's response to CBER IR request (STN 125163/405.6). The numerical accuracy was verified by the reviewer.

Table 4: Difference in SCRs (F-QIV - Q-QIV) at 28 days after the last vaccine dose, by age

Strain	**6-23 months** Difference in SCRs (95% CI)	**24-35 months** Difference in SCRs (95% CI)
H1N1	-5.8 (-11.3, -0.4)	-7.8 (-13.6, -1.9)
H3N2	-6.3 (-11.5, -1.2)	-7.5 (-13.6, -1.4)
B/Yamagata	-15.6 (-20.3, -10.8)	-6.5 (-11.7, -1.3)
B/Victoria	-21.1 (-26.6, -15.5)	-9.3 (-16.1, -2.3)

Source: Extracted from Table 18 in the applicant's response to CBER IR request (STN 125163/405.6). The numerical accuracy was verified by the reviewer.

Table 5: GMT ratios (F-QIV/Q-QIV), adjusted for baseline titer, at 28 days after the last vaccine dose, by sex

Strain	**Female** GMT ratio (95% CI)	**Male** GMT ratio (95% CI)
H1N1	0.83 (0.71, 0.96)	0.88 (0.76, 1.01)
H3N2	0.84 (0.73, 0.98)	0.85 (0.74, 0.97)
B/Yamagata	0.64 (0.56, 0.73)	0.65 (0.58, 0.74)
B/Victoria	0.60 (0.52, 0.70)	0.63 (0.55, 0.73)

Source: Extracted from Table 13 in the applicant's response to CBER IR request (STN 125163/405.6). The numerical accuracy was verified by the reviewer.

Table 6: Difference in SCRs (F-QIV - Q-QIV) at 28 days after the last vaccine dose, by sex

Strain	**Female** Difference in SCRs (95% CI)	**Male** Difference in SCRs (95% CI)
H1N1	-6.7 (-12.5, -0.8)	-6.0 (-11.6, -0.5)
H3N2	-6.2 (-11.9, -0.6)	-7.3 (-12.8, -1.8)
B/Yamagata	-12.4 (-17.4, -7.4)	-11.3 (-16.3, -6.4)
B/Victoria	-17.4 (-23.6, -11.1)	-15.6 (-21.5, -9.5)

Source: Extracted from Table 17 in the applicant's response to CBER IR request (STN 125163/405.6). The numerical accuracy was verified by the reviewer.

The subgroup analyses of fever (≥38C; overall/dose) during the 7-day post-vaccination period by age and sex are shown in Table 7. Subgroup analysis of fever (≥38C; overall/dose) during the 7-day post-vaccination period by ethnicity is not shown because the majority (~80%) of the subjects were either white or black. Moreover, there was no difference observed between white and black subjects in terms of fever (≥38C; overall/dose) during the 7-day post-vaccination period. Subgroup analysis of fever (≥38C; overall/dose) during the 7-day post-vaccination period by country was not shown because the majority (>90%) of the subjects were from the US.

Table 7: Incidence of fever (≥38C; overall/dose) during the 7-day post-vaccination period, by age and sex

		F-QIV	Q-QIV
Age	6-23 months	5.6%	6.3%
	24-35 months	5.0%	4.8%
Sex	Female	5.2%	6.3%
	Male	5.6%	5.4%

Source: Extracted from Tables 9 and 10 in the applicant's response to CBER IR request (STN 125163/405.6). The numerical accuracy was verified by the reviewer.

7. Integrated Overview of Efficacy

N/A

8. Integrated Overview of Safety

N/A

10. Conclusions

Among the subjects in this study (6-35 months of age), Q-QIV appears to be immunogenically non-inferior to F-QIV, in terms of GMT ratio and SCR difference for all four strains contained in the vaccine, as shown in Tables 1 and 2 in section 6.1.11.1.

The safety profile of Q-QIV appears to be comparable to F-QIV in terms of SAEs and fever. However, ~2% of the fever observations were ≤35C, which the applicant claimed to be "mishandling by the parents." Whether this "mishandling by the parents" was restricted to fever observations ≤35C or was a systematic problem across all fever observations is not verifiable. However, no significant difference in the distribution of fever between the two groups was observed.