



Statistical Review and Evaluation BLA

BLA/Supplement Number: STN 125163/253

Product Name: FluLaval® quadrivalent influenza vaccine

Indication(s): Active immunization against disease caused by influenza virus subtypes A and both influenza B lineages contained in the vaccine

Applicant: ID Biomedical Corporation of Quebec / GSK

Date(s): Submission Date: 10/16/2012
Action Due Date: 8/16/2013

Review Priority: Standard

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1. EXECUTIVE SUMMARY

1.1 Introduction

This application is in support of indication of a multi-dose, thimerosal-containing formulation of FluLaval Quadrivalent Influenza Vaccine (Q-QIV T+) for individuals 3 years of age and older. This BLA submission contains the results from three Phase III IND studies (Q-QIV-003, Q-QIV-006, and Q-QIV-007), and one non-IND study Q-QIV-009 (n=112, single arm). This review focuses on Q-QIV-003, Q-QIV-006, and Q-QIV-007.

1.2 Brief Overview of Clinical Studies

This license application for FluLaval Quadrivalent Influenza Vaccine (Q-QIV T+) for individuals 3 years of age and older included efficacy, immunogenicity, and safety data obtained from three Phase III IND studies and one non-IND study. A summary of the three Phase III IND studies is given in Table 1.

Table 1. Summary of submitted studies

Study Identifier	Location	Population	Objectives	Design	Vaccine	# of Subjects
Q-QIV-003	Canada, Mexico, Spain, Taiwan, US	Children in stable health 6 months – 17 years of age	Immunogenic noninferiority of Q-QIV to TIV in children 3-17 years of age; Immunogenicity of Q-QIV in children 6-35 months of age; Reactogenicity and safety	Double-Blind Randomized, Active Controlled, Phase III, Multi-center	3-17 years of age: Q-QIV TIV-VB TIV-YB 6-35 months of age: Q-QIV	932 929 932 301
Q-QIV-006	Bangladesh, Dominican Republic, Honduras, Lebanon, Panama, Philippines, Thailand, Turkey	Children in stable health 3 – 8 years of age	Efficacy of Q-QIV compare to a non-influenza vaccine; Reactogenicity and safety	Observer-Blind, Randomized, Controlled, Phase III, Multi-center	Q-QIV Havrix	2584 2584
Q-QIV-007	Canada, Mexico, US	Adults in stable health 18 years and older	Lot-to-lot consistency of 3 lots of Q-QIV; Immunogenic noninferiority of Q-QIV to TIV; Reactogenicity and safety	Double-Blind Randomized, Active Controlled, Phase III, Multi-center	Q-QIV (lot 1) Q-QIV (lot 1) Q-QIV (lot 1) TIV-VB TIV-YB	423 424 425 213 218

1.3 Regulatory History

FluLaval is currently licensed under the Accelerated Approval Regulations (21 CFR 601.41) for individuals 18 years and older, in a thimerosal-containing multi-dose (10 doses) vial presentation. With this submission, the applicant is seeking approval of a multi-dose, thimerosal-containing formulation of FluLaval Quadrivalent Influenza Vaccine (Q-QIV T+) for individuals 3 years of age and older.

1.4 Conclusions and Major Statistical Issues

All three studies were performed as pre-specified. Primary efficacy/immunogenicity objectives of each study (absolute efficacy of Q-QIV, immunogenic noninferiority of Q-QIV to TIV, lot consistency of 3 lots of Q-QIV) were met. Based on the reactogenicity and safety profile, Q-QIV seemed to be well tolerated. No major statistical issue was identified.

2. INTRODUCTION

2.1 Background Information

This BLA submission included Clinical Study Reports for three clinical studies, Q-QIV-003, Q-QIV-006, and Q-QIV-007 with relevant datasets. These studies had the following objectives:

- Demonstration of vaccine efficacy and immunogenicity based on clinical and surrogate endpoints
- Demonstration of safety as compared to TIV and Placebo.
- Demonstration of lot-to-lot consistency.

2.2 Data Sources

The clinical study reports (CSRs) as well as other related materials were provided by the applicant. SAS transport datasets were also submitted in this submission.

2.3 Material Reviewed

This statistical review is based on the clinical study reports (three pivotal studies), and datasets included in this submission STN 125163/253, Module 5 Section 5.3.5.1.

3. STATISTICAL EVALUATION OF EFFICACY AND IMMUNOGENICITY DATA

3.0 List of Studies

This BLA submission contains the results from three Phase III IND studies (Q-QIV-003, Q-QIV-006, and Q-QIV-007) and one non-IND study Q-QIV-009 (n=112, single arm). This review focuses on Q-QIV-003, Q-QIV-006, and Q-QIV-007.

3.1 Study Q-QIV-006

3.1.1 Brief Overview of the Study

This was a Phase III, observer blind, randomized, non-influenza vaccine (Havrix) comparator-controlled, multi-country (8 countries) and multi-center (15 centers) study to evaluate the efficacy of GSK Biologicals' quadrivalent, inactivated, split virion, seasonal influenza vaccine candidate, GSK2282512A (FLU Q-QIV), administered intramuscularly in healthy children 3 to 8 years of age.

Two treatment groups were as follows:

- [Q-QIV] Investigational Quadrivalent Influenza Vaccine (n=2,600 planned)
- [Havrix] non-influenza vaccine control (n=2,600 planned).

Hepatitis A virus vaccine, Havrix, was used as an active control in this study rather than placebo, to provide potential benefit to children who were in the control arm.

The primary efficacy objective of this study was to evaluate the efficacy of Q-QIV in the prevention of reverse transcriptase polymerase chain reaction (RT-PCR) confirmed influenza A and/or B disease presenting as influenza-like illness (ILI), compared to a non-influenza vaccine comparator (Havrix) in children 3 to 8 years of age. The primary efficacy objective will be considered met if the lower bound of the 2-sided 95% CI of the VE is >30%.

3.1.2 Evaluation of Efficacy Results

A total of 5,175 subjects were enrolled; 2,587 were vaccinated with Q-QIV and 2,588 were vaccinated with Havrix. The primary efficacy analysis was performed on the Per-Protocol cohort (Q-QIV: 2,379; Havrix: 2,398). The applicant performed the primary efficacy analyses as pre-specified, and the applicant's results in Table 2 were verified by the reviewer.

Table 2. Vaccine efficacy for RT-PCR confirmed influenza A and/or B disease presenting as ILI reported from 14 days post-vaccination through the end of ILI surveillance period

Age Group	Treatment	Attack Rate	VE*	95% CI of VE
3-8 years of age	Q-QIV	2.44% (58/2379)	55.4%	(39.1;67.3)
	Havrix	5.34% (128/2398)		

*VE was based on Cox regression, adjusted for age (3-4y/5-8y), region, and priming status as covariates.

Reviewer’s comment: As shown in Table 2, the primary efficacy objective was met (the lower bound of the 2-sided 95% CI of the VE is >30%).

3.1.3 Subgroup analyses by Age, Gender, Race and Study Site

As shown in Table 3, VE in 3-4 years of age subjects was lower when compared to 5-8 years of age subjects.

Table 3. Vaccine efficacy for RT-PCR confirmed influenza A and/or B disease presenting as ILI reported from 14 days post-vaccination through the end of ILI surveillance period by age group

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

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

(Post hoc) subgroup analyses of efficacy by gender, race, or country (Bangladesh, Dominican Republic, Honduras, Lebanon, Panama, Philippines, Thailand, and Turkey) did not show any remarkable difference in vaccine efficacy of Q-QIV between genders, race groups, or countries. All subjects from one study site (n= 45, 0.9% of all enrolled subjects) in Turkey were not included in efficacy and safety analysis due to significant compliance violations. However, no RT-PCR confirmed influenza A and/or B disease presenting as ILI reported from 14 days post-vaccination through the end of ILI surveillance period was reported from this study site.

3.2. Study Q-QIV-003

3.2.1 Brief Overview of the Study

This was a Phase III, double blind, randomized, multi-country (5 countries) and multi-center (32 centers) study to evaluate the immunogenicity and safety of GSK Biologicals’ quadrivalent influenza vaccine candidate, GSK2282512A (FLU Q-QIV), compared to GSK Biologicals’ trivalent influenza vaccine Fluarix® administered intramuscularly to children 3 to 17 years of age. (Children 6-35 months of age were also enrolled in this study, and all of them were vaccinated with FLU Q-QIV to describe the safety and immunogenicity of FLU Q-QIV in an exploratory manner. Safety and immunogenicity

analyses for children 6-35 months of age will not be included in this review because the applicant is seeking an indication of Q-QIV for use in persons 3 years of age and older).

Three treatment groups were as follows:

[Q-QIV] Investigational Quadrivalent Influenza Vaccine (n=900 planned)

[TIV-VB] Fluarix-VB (TIV containing Victoria B strain) (n=900 planned)

[TIV-YB] Fluarix-VB (TIV containing Yamagata B strain) (n=900 planned).

The primary immunogenicity objective of this study was to evaluate the immunogenic non-inferiority (in terms of Geometric Mean Titer [GMT] and Seroconversion Rate [SCR]) for the shared viral strains of Q-QIV versus TIV-VB and TIV-YB in children 3 to 17 years old approximately 28 days after completion of dosing (approximately at Day 28 for primed subjects and approximately at Day 56 for unprimed subjects). Criteria to conclude non-inferiority of Q-QIV were (a) the upper bound of the two-sided 95% confidence interval of the GMT ratio (TIV / Q-QIV) does not exceed 1.5 for each of the three strains (H1N1, H3N2, and shared B, i.e., VB or YB), and (b) the upper bound of the two-sided 95% confidence interval for the difference in SCR (TIV minus Q-QIV) does not exceed 10% for each of the three strains. The comparators were subjects in the two Fluarix groups [TIV-VB and TIV-YB] combined for H1N1 and H3N2 strains and subjects who received Fluarix with a matching B strain for the Victoria B and Yamagata B strains.

3.2.2 Evaluation of Immunogenicity Results

3.2.2.1 Evaluation of Primary Immunogenicity Results

A total of 2,807 subjects were enrolled; 932 were vaccinated with Q-QIV, 929 were vaccinated with TIV-VB, and 932 were vaccinated with TIV-YB. The primary immunogenicity analysis was performed on the Per-Protocol cohort (Q-QIV: 878; TIV-VB: 871; TIV-YB: 878). The applicant performed the primary immunogenicity analyses as pre-specified, and the applicant's results in Tables 4 and 5 were verified by the reviewer. (Confidence intervals for the GMT ratios were calculated based on the normality assumption of log titers, and confidence intervals for the seroconversion rate differences were calculated based on the normal approximation to the binomial distribution.)

Table 4. Primary immunogenicity results for children 3-17 years of age: GMT ratio

Antigen strain	Treatment Group	n	GMT	GMT ratio[TIV/Q-QIV] (95% CI)	Non-inferiority of QIV to TIV (UB of CI of GMT ratio < 1.5)
H1N1	TIV-VB+TIV-YB	1747	421.4	1.15 (1.06; 1.25)	Yes
	Q-QIV	876	366.3		
H3N2	TIV-VB+TIV-YB	1746	144.3	0.99 (0.92; 1.07)	Yes
	Q-QIV	876	145.8		
Victoria B	TIV-VB	870	243.4	0.96 (0.87; 1.07)	Yes
	Q-QIV	876	252.5		
Yamagata B	TIV-YB	877	564.6	1.08 (0.99; 1.16)	Yes
	Q-QIV	876	525.2		

Table 5. Primary immunogenicity results for children 3-17 years of age: Seroconversion Rate (SCR) difference

Antigen strain	Treatment Group	n	SCR(%)	SCR(%) difference [TIV minus Q-QIV] (95% CI)	Non-inferiority of QIV to TIV (UB of CI of SCR difference < 10%)
H1N1	TIV-VB+TIV-YB	1747	86.1	1.79 (-1.04; 4.77)	Yes
	Q-QIV	876	84.4		
H3N2	TIV-VB+TIV-YB	1746	68.7	-1.36 (-5.05; 2.41)	Yes
	Q-QIV	876	70.1		
Victoria B	TIV-VB	870	71.5	-3.05 (-7.21; 1.12)	Yes
	Q-QIV	876	74.5		
Yamagata B	TIV-YB	877	73.4	-1.80 (-5.89; 2.30)	Yes
	Q-QIV	876	75.2		

Reviewer's comment: As shown in Tables 4 and 5, the primary immunogenicity objective was met.

3.2.2.2 Evaluation of Secondary Immunogenicity Results

For Victoria B and Yamagata B strains, the statistical criteria to show higher immune response to Q-QIV compared to TIV were that the lower bound for each of the two 95% CIs for the GMT ratios (Q-QIV/TIV) be > 1.5, and the lower bound for each of the two 95% CIs for the seroconversion rate differences (Q-QIV minus TIV) be > 10.0%. The comparators were subjects who did not receive TIV with a matching B strain.

The secondary immunogenicity analyses were performed on the Per-Protocol population. The applicant performed the secondary immunogenicity analyses as pre-specified, and the applicant's results (Tables 6-7) were verified by the reviewer. (Confidence intervals for the GMT ratios were calculated based on the normality assumption of log titers, and

confidence intervals for the seroconversion rate differences were calculated based on the normal approximation to the binomial distribution.)

Table 6. Secondary immunogenicity results for children 3-17 years of age: GMT ratio

Antigen strain	GMT ratio[Q-QIV/TIV] (95% CI)	Higher Response to QIV vs. TIV (LB of CI of GMT ratio > 1.5)
Victoria B	3.78 (3.43; 4.16)	Yes
Yamagata B	2.61 (2.41; 2.84)	Yes

* For Victoria B, GMT ratio of Q-QIV/TIV-YB. For Yamagata B, GMT ratio of Q-QIV/ TIV-VB

Table 7. Secondary immunogenicity results for children 3-17 years of age:
Seroconversion Rate (SCR) difference

Antigen strain	SCR(%) difference[Q-QIV minus TIV] (95% CI)	Higher Response to QIV vs. TIV (LB of CI of SCR difference > 10%)
Victoria B	44.63 (40.35; 48.72)	Yes
Yamagata B	33.96 (29.55; 38.24)	Yes

* For Victoria B, SCR difference of Q-QIV minus TIV-YB. For Yamagata B, SCR difference of Q-QIV minus TIV-VB

Reviewer's comment: As shown in Tables 6 and 7, the secondary immunogenicity objective was met.

3.2.3 Subgroup analyses by Age, Gender, Race, and Study Sites

(Post hoc) subgroup analyses of immunogenicity by age (3-8 years and 9-17 years) gender, race, or country (Canada, Mexico, Spain, Taiwan, and the United States) did not show any remarkable difference in immunogenic non-inferiority of Q-QIV compared to TIV between the age groups, genders, race groups, or countries.

3.3. Study Q-QIV007

3.3.1 Brief Overview of the Study

This was a Phase III, double blind, randomized, multi-country (3 countries) and multi-center (12 centers) study to evaluate the immunogenicity and safety of GSK Biologicals' quadrivalent influenza vaccine candidate, GSK2282512A (FLU Q-QIV) when administered intramuscularly to adults 18 years of age and older.

Five treatment groups are as follows:

- [Q-QIV Lot 1] Investigational Quadrivalent Influenza Vaccine from Lot 1 (n=400 planned)
- [Q-QIV Lot 2] Investigational Quadrivalent Influenza Vaccine from Lot 2 (n=400 planned)
- [Q-QIV Lot 3] Investigational Quadrivalent Influenza Vaccine from Lot 3 (n=400 planned)
- [TIV-VB] FluLaval-VB (TIV containing Victoria B strain) (n=200 planned)
- [TIV-YB] FluLaval-VB (TIV containing Yamagata B strain) (n=200 planned).

The primary immunogenicity objective of this study was to evaluate lot-to-lot consistency (in terms of Geometric Mean Titer [GMT]) of three lots of Q-QIV for each of the four strains, 21 days after intramuscular vaccination of adults 18 years and older. The statistical criterion for lot consistency with respect to GMTs required that the two-sided 95% CI on the ratio of GMTs between any pair of the three lots be entirely within (1/1.5, 1.5) for each strain.

3.3.2 Evaluation of Immunogenicity Results

3.3.2.1 Evaluation of Primary Immunogenicity Results

A total of 1,707 subjects were enrolled; 1,272 were vaccinated with Q-QIV (Lot 1; 423, Lot 2; 424, Lot 3; 425), 213 were vaccinated with TIV-VB, and 218 were vaccinated with TIV-YB. The primary immunogenicity analysis of lot consistency was performed on the Per-Protocol cohort of Q-QIV recipients (Lot 1; 414, Lot 2; 416, Lot 3; 416). The lot consistency results in Table 8 were prepared by the reviewer. (Confidence intervals for the GMT ratios were calculated based on the normality assumption of log titers.)

Table 8. Lot consistency analyses by antigen strain

Antigen strains		GMT ratio (95% CI)
H1N1	Lot 1 / Lot 2	1.05 (0.88; 1.24)
	Lot 1 / Lot 3	0.94 (0.79; 1.12)
	Lot 2 / Lot 3	0.90 (0.75; 1.07)
H3N2	Lot 1 / Lot 2	1.08 (0.92; 1.27)
	Lot 1 / Lot 3	1.00 (0.85; 1.17)
	Lot 2 / Lot 3	0.92 (0.78; 1.08)
Victoria B	Lot 1 / Lot 2	0.97 (0.84; 1.11)
	Lot 1 / Lot 3	1.03 (0.90; 1.18)
	Lot 2 / Lot 3	1.06 (0.92; 1.23)
Yamagata B	Lot 1 / Lot 2	1.07 (0.93; 1.22)
	Lot 1 / Lot 3	1.09 (0.95; 1.25)
	Lot 2 / Lot 3	1.02 (0.89; 1.17)

Reviewer’s comment: As shown in Table 8, the primary immunogenicity objective was met.

3.3.2.2 Evaluation of Secondary Immunogenicity Results

The secondary immunogenicity analysis was performed on the Per-Protocol cohort (Q-QIV: 1,246; TIV-VB: 204; TIV-YB: 211). The applicant performed the secondary immunogenicity analyses as pre-specified, and the applicant’s results in Tables 9 and 10 were verified by the reviewer. (Confidence intervals for the GMT ratios were calculated based on the normality assumption of log titers.)

3.3.2.2.1 Immunogenic non-inferiority of Q-QIV compared to TIV

The criterion to conclude non-inferiority of Q-QIV was that the upper bound of the two-sided 95% confidence interval of the GMT ratio (TIV / Q-QIV) does not exceed 1.5 for each of the three strains (H1N1, H3N2, and shared B, i.e., VB or YB). The comparators were subjects in the two TIV groups [TIV-VB and TIV-YB] combined for H1N1 and H3N2 strains and subjects who received TIV with a matching B strain for the Victoria B and Yamagata B strains.

Table 9. Secondary immunogenicity results for subjects 18 years and older: GMT ratio

Antigen strain	GMT ratio[TIV/Q-QIV] (95% CI)	Non-inferiority of QIV to TIV (UB of CI of GMT ratio < 1.5)
H1N1	0.78 (0.68; 0.90)	Yes
H3N2	1.19 (1.05; 1.35)	Yes
Victoria B	0.75 (0.65; 0.87)	Yes
Yamagata B	0.79 (0.69; 0.90)	Yes

* For Victoria B, GMT ratio of TIV-VB/Q-QIV. For Yamagata B, GMT ratio of TIV-YB/Q-QIV

3.3.2.2.2 Immunogenic enhancement of Q-QIV compared to TIV for the B strain not included in each TIV vaccine

For Victoria B and Yamagata B strains, the statistical criterion to show higher immune response to Q-QIV compared to TIV was that the lower bound for each of the two 95% CIs for the GMT ratios (Q-QIV/TIV) be > 1.5. The comparators were subjects who did not receive TIV with a matching B strain.

Table 10. Secondary immunogenicity results for subjects 18 years and older: GMT ratio

Antigen strain	GMT ratio[Q-QIV/TIV] (95% CI)	Higher Response to QIV vs. TIV (LB of CI of GMT ratio > 1.5)
Victoria B	2.44 (2.11; 2.83)	Yes
Yamagata B	2.18 (1.90; 2.51)	Yes

* For Victoria B, GMT ratio of Q-QIV/TIV-YB. For Yamagata B, GMT ratio of Q-QIV/ TIV-VB

Reviewer's comment: As shown in Tables 9 and 10, the secondary immunogenicity objective was met.

3.3.3 Subgroup analyses by Age, Gender, Race, and Study Sites

(Post hoc) subgroup analyses of immunogenicity by age (18-64 years and 65 years and older), gender, race, or country (Canada, Mexico, and the United States) did not show any remarkable difference in lot consistency among three lots of Q-QIV between the age groups, genders, race groups, or countries. However, these subgroup analyses have limitations due to the small sample size in each lot (~400).

4. Statistical Evaluations of Safety Data

4.1 Study Q-QIV-006

The safety analyses were performed on the Total Vaccinated cohort (Q-QIV: 2,584; Havrix: 2,584). There were 43 SAEs reported by 36 subjects in the Q-QIV group (1.39% of subjects who received Q-QIV) and 29 SAEs reported by 24 subjects in the Havrix group (0.93% of subjects who received Havrix). For individual list of SAEs and further details, please see the clinical review.

Two deaths were reported (both were drowning), one in each treatment group, but neither was deemed by the applicant to be causally related to vaccination. There was one non-fatal SAE (bronchitis) in the Q-QIV group that was deemed by the study applicant to be causally related to vaccination. The SAE occurred in a 7-year old male subject on the day of the second dose of vaccine, lasted for 10 days, and was reported as recovered/resolved. Since there was only one SAE (in the Q-QIV group) reported as causally related to vaccination, subgroup analysis was not performed.

4.2 Study Q-QIV-003

Among the 3 to 17 year old subjects, the safety analyses were performed on the Total Vaccinated cohort (Q-QIV: 932; TIV-VB: 929; TIV-YB: 932). There were 4 SAEs reported by 3 subjects in the Q-QIV group (0.32% of subjects who received Q-QIV), 12 SAEs reported by 6 subjects in the TIV-VB group (0.65% of subjects who received TIV-VB), and 9 SAEs reported by 5 subjects in the TIV-YB group (0.54% of subjects who received TIV-YB). For individual list of SAEs and further details, please see the clinical review.

One subject in TIV-YB group (PID 5159) had two SAEs (angioedema and conjunctivitis) which were considered by the applicant to be related to the vaccine. No death was reported. Since there were only two SAEs (from one subject in the TIV-YB group) reported as causally related to vaccination, subgroup analysis was not performed.

4.3 Study Q-QIV007

The safety analyses were performed on the Total Vaccinated cohort (Q-QIV: 1,272; TIV-VB: 213; TIV-YB: 218). Thirty-five (35) subjects in the Q-QIV group (2.75% of subjects who received Q-QIV), 3 subjects in the TIV-VB group (1.41% of subjects who received TIV-VB), and 7 subjects in the TIV-YB group (3.21% of subjects who received TIV-YB) reported SAEs.

For individual list of SAEs and further details, please see the clinical review.

Fatal SAEs were reported for 7 subjects: 5 (0.39%; 2 cardiac disorders, 1 lung cancer, 1 metastatic neoplasm, and 1 stab wound/cardiac disorder) in the Q-QIV group and 2

(0.92%; 1 hepatic cirrhosis/portal hypertension, and 1 hip fracture) in the TIV-YB group. No SAEs were assessed by the applicant to be causally related to study vaccine.

5. Final Conclusions

All three studies were performed as pre-specified. Primary efficacy/immunogenicity objectives of each study (absolute efficacy of Q-QIV, immunogenic noninferiority of Q-QIV to TIV, lot consistency of 3 lots of Q-QIV) were met. Based on the reactogenicity and safety profile, Q-QIV seemed to be well tolerated. No major statistical issue was identified.

6. Distribution List

ChronFile/HFM-210
Santosh Nanda/Edward Wolfgang/HFM-478
Roshan Ramanathan/Melisse Baylor /HFM-475
John Scott/Estelle Russek-Cohen/HFM-215