DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

Statistical Review and Evaluation
BLA

BLA/Supplement Number:	STN 125163/254
Product Name:	FluLaval® influenza vaccine
Indication(s):	Active immunization against disease caused by influenza virus subtypes A and B contained in the vaccine
Applicant:	ID Biomedical Corporation of Quebec / GSK
Date(s):	Submission Date: 10/18/2012 Action Due Date: 8/16/2013
Review Priority:	Standard
Statistical Branch:	Vaccine Evaluation Branch (VEB)
Primary Statistical Reviewer:	Sang Ahnn
Through:	Tsai-Lien Lin, Team Leader Viral and Bioassay Team, VEB Dale Horne, Branch Chief Vaccine Evaluation Branch
Medical Office/Division:	OVRR/DVRPA
Clinical Reviewer(s):	Roshan Ramanathan, Melisse Baylor
Project Manager(s):	Bernard McWatters, Laura Montague

Table of Contents

List of Tables

1. EXECUTIVE SUMMARY

1.1 Introduction

This application is in support of indication of FluLaval for individuals 3 to 17 years of age. This BLA submission contains the results from a Phase III study, FLU Q-TIV-(b)(4)-008.

1.2 Brief Overview of the Clinical Study

Study FLU Q-TIV-(b)(4)-008 included safety and immunogenicity data. A summary of the study is given in Table 1.

Table 1: General summary of submitted study

Study Identifier	Location	Population	Objectives	Design	Vaccine	# of Subjects
Q-TIF-(b)(4)-008	US	Healthy Children 3 to 17 years of age	Immunogenic non-inferiority of FluLaval (b)(4) to Fluzone; Reactogenicity and safety	Double-Blind Randomized, Active Controlled, Phase III, Multi-center	FluLaval (b)(4) Fluzone	1055 1061

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 an indication of FluLaval for individuals 3 to 17 years of age.

1.4 Conclusions and Major Statistical Issues

Study FLU Q-TIV-(b)(4)-008 was performed as pre-specified. The primary immunogenicity objective was met [immunogenic non-inferiority (in terms of Geometric Mean Titer [GMT] and Seroconversion Rate [SCR]) of FluLaval (b)(4) compared to Fluzone in children 3 to 17 years old]. FluLaval (b)(4) and Fluzone appear to have similar safety profiles in children 3 to 17 years old. No major statistical issue was identified.

2. INTRODUCTION

2.1 Background Information

This BLA submission included Clinical Study Reports for study FLU Q-TIV-(b)(4)-008 with relevant datasets. This study had the following objectives:

- Demonstration of immunogenic non-inferiority of FluLaval (b)(4) to Fluzone with respect to surrogate endpoints.
- Demonstration of safety of FluLaval (b)(4) as compared to Fluzone.

2.2 Data Sources

The clinical study report (CSR) 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 report of study FLU Q-TIV-(b)(4)-008, and datasets included in this submission STN 125163/254.

3. STATISTICAL EVALUATION OF IMMUNOGENICITY DATA

3.1 Study Q-TIV-(b)(4)-008

3.1.1 Brief Overview of the Study

This is a phase III, observer-blind, multi-center (30 centers in the U.S.), randomized study to evaluate the immunogenicity and safety of FluLaval (b)(4) (GSK Biologicals) compared with Fluzone (Sanofi-Pasteur, Inc.) administered intramuscularly in children 3 to 17 years of age in the United States.

Two treatment groups are as follows:
[FluLaval (b)(4)] Investigational Influenza Vaccine (n=1,050 planned)
[Fluzone] Influenza vaccine control (n=1,050 planned)

The primary immunogenicity objective of this study is to evaluate the immunogenic non-inferiority (in terms of Geometric Mean Titer [GMT] and Seroconversion Rate [SCR]) of FluLaval (b)(4) versus Fluzone 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 FluLaval (b)(4) are (a) the upper bound of the two-sided 95% confidence interval of the GMT ratio (Fluzone / FluLaval (b)(4)) does not exceed 1.5 for each of the three strains, and (b) the upper bound of the two-sided 95% confidence interval for the difference in SCR (Fluzone minus FluLaval (b)(4)) does not exceed 10% for each of the three strains.

3.1.2 Evaluation of Immunogenicity Results

A total of 2,128 subjects were enrolled, and randomized (1:1 ratio), stratified by investigator site and age group（3 to 4 years, 5 to 8 years, and 9 to 17 years old); 1,055 were vaccinated with FluLaval (b)(4) and 1,061 with Fluzone. The Per-Protocol (PP) cohort for immunogenicity included 987 subjects in the FluLaval (b)(4) group, and 978 subjects in the Fluzone group.

The primary immunogenicity analyses were performed on the Per-Protocol cohort. The applicant performed the primary immunogenicity analyses as pre-specified, and the applicant's results in Tables 2 and 3 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 2. Primary immunogenicity results for all age groups (3 - 17 years of age): GMT ratio

Antigen strain	Treatment Group	n	GMT	GMT ratio* (95% CI)	Non-inferiority of FluLaval (b)(4) to Fluzone (UB of 95% CI of GMT ratio* < 1.5)
A/Brisbane	Fluzone	978	346.9	1.03 (0.94; 1.13)	Yes
	FluLaval-(b)(4)	987	337.5		
A/Uruguay	Fluzone	978	452.6	1.05 (0.96; 1.13)	Yes
	FluLaval-(b)(4)	987	432.8		
B/Brisbane	Fluzone	978	204.0	0.93 (0.85; 1.02)	Yes
	FluLaval-(b)(4)	987	218.8		

* GMT ratio of Fluzone/FluLaval -(b)(4)

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

Antigen strain	Treatment Group	n	SCR(%)	SCR(%) difference* (95% CI)	Non-inferiority of FluLaval (b)(4) to Fluzone (UB of 95% CI of SCR difference* < 10%)
A/Brisbane	Fluzone	978	58.2	-1.6 (-5.9; 2.8)	Yes
	FluLaval-(b)(4)	987	59.8		
A/Uruguay	Fluzone	978	66.2	-2.0 (-6.2; 2.1)	Yes
	FluLaval-(b)(4)	987	68.2		
B/Brisbane	Fluzone	978	78.6	-2.4 (-6.0; 1.1)	Yes
	FluLaval-(b)(4)	987	81.1		

* SCR difference of Fluzone - FluLaval -(b)(4)

Reviewer's comment: As shown in Tables 2 and 3, the primary immunogenicity objective was met.

3.1.3 Subgroup analyses by age, gender, race, and study site

(Post hoc) subgroup analyses of immunogenicity by age (3 to 4 years, 5 to 8 years, and 9 to 17 years old), gender, race, or study site (30 US sites) did not show any remarkable difference in immunogenic noninferiority of FluLaval (b)(4) compared to Fluzone between the age groups, genders, race groups, or study sites.

4. Statistical Evaluations of Safety Data

4.1 Study Q-TIV-(b)(4)-008

The safety analyses were performed on the Total vaccinated cohort (FluLaval (b)(4): 1,055; Fluzone: 1,061). There were 15 SAEs reported by 10 subjects in the FluLaval (b)(4) group (0.95% of subjects who received FluLaval (b)(4)) and 9 SAEs reported by 6 subjects in the Fluzone group (0.57% of subjects who received Fluzone). Please see Appendix for more details.

Two SAEs (insulin-dependent diabetes mellitus in the Fluzone group and seizure disorder/convulsion in the FluLaval (b)(4) group) were reported as causally related to vaccination and neither SAE had been resolved by the end of the study. No fatal SAEs were reported. Since there were only two SAEs (one in each group) reported as causally related to vaccination, subgroup analysis was not performed.

5. Final Conclusions

Study FLU Q-TIV-(b)(4)-008 was performed as pre-specified. The primary immunogenicity objective was met [immunogenic non-inferiority (in terms of Geometric Mean Titer [GMT] and Seroconversion Rate [SCR]) of FluLaval (b)(4) compared to Fluzone in children 3 to 17 years old]. FluLaval (b)(4) and Fluzone appear to have similar safety profiles in children 3 to 17 years old. No major statistical issue was identified.

6. Distribution List

ChronFile/HFM-210
Bernard McWatters/Laura Montague/HFM-478
Roshan Ramanathan/Melisse Baylor /HFM-475
John Scott/Estelle Russek-Cohen/HFM-215

Appendix

Table 4. Listing of all SAEs

Subject ID	Vaccine	Age	Gender	Verbatim	Preferred Term	Outcome
1	FluLaval-(b)(4)	9	M	Incisional abscess-right shoulder	Abscess	Recovered/resolved
984	FluLava-(b)(4)	4	M	Cellulitis to the right foot	Cellulitis	Recovered/resolved
1003	FluLaval-(b)(4)	5	M	Possible mood disorder	Affective disorder	Recovered/resolved
		5		Adhd	Attention deficit/hyperactivity disorder	Recovered/resolved
		5		Oppositional defiant disorder	Oppositional defiant disorder	Recovered/resolved
1242	FluLaval-(b)(4)	3	M	Pneumonia	Pneumonia	Recovered/resolved
1909	FluLaval-(b)(4)	6	F	Fracture to left distal radius and ulna	Forearm fracture	Recovered/resolved
2453	FluLaval-(b)(4)	14	F	Vomiting	Vomiting	Recovered/resolved
2962	FluLaval-(b)(4)	3	M	Coxsackie viral herpangina	Herpangina	Recovered/resolved
		3		Oral candidiasis	Oral candidiasis	Recovered/resolved
3141	FluLaval-(b)(4)	6	M	Influenza h1n1	H1N1 influenza	Recovered/resolved
		6		Bilateral pneumonia	Pneumonia	Recovered/resolved
		6		Respiatory distress	Respiratory distress	Recovered/resolved
3366	FluLaval-(b)(4)	17	F	Seizure disorder	Convulsion	Not recovered/not resolved
3967	FluLaval-(b)(4)	13	M	Appendicitis	Appendicitis	Recovered/resolved

1002	Fluzone	3	M	Bronchiolitis	Bronchiolitis	Not recovered/not resolved
1077	Fluzone	8	F	Gastroenteritis	Gastroenteritis	Recovered/resolved
2348	Fluzone	4	M	Insulin dependent diabetes mellitus	Type 1 diabetes mellitus	Not recovered/not resolved
2963	Fluzone	6	F	Coxsackie viral herpangina	Herpangina	Recovered/resolved
		6		Oral candidiasis	Oral candidiasis	Recovered/resolved
3980	Fluzone	10	M	Sinus polyps	Sinus polyp	Recovered/resolved
4136	Fluzone	4	F	Asthma exacerbation	Asthma	Recovered/resolved
		4		Hypoxemia	Hypoxia	Recovered/resolved
		4		Pneumonia	Pneumonia	Recovered/resolved