DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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: 125254/132

Product Name: Afluria (CSL Seasonal Flu Vaccine)

Indication(s): Active immunization of persons ages 6 months to 18 years old against influenza disease caused by influenza virus subtypes A and type B present in the vaccine

Applicant: CSL, Limited

Date(s): September 11, 2009

Review Priority: Accelerated

Statistical Branch: Vaccine Evaluation Branch

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1. EXECUTIVE SUMMARY

This submission includes a Prior Approval Supplement (PAS STN 125254/132) which contains data and summarization of immunogenicity and safety responses from a single pediatric study, Study CSLCT-FLU-04-05 entitled, "An Open-Label, Multi-Centre Study to Evaluate the Safety, Tolerability and Immunogenicity of CSL's Influenza Vaccine in a Paediatric Population (≥ 6 months to < 9 years of age)," performed by CSL in Australia. In this small open label study (n=298), children in two different age groups from 6 months to 9 years of age inclusive were enrolled in the study.

Children in both age groups: 6 months to 3 years of age and 3 years to 9 years of age, met both immune response endpoints (seroconversion and seroprotection) recommended in the FDA May 2007 Guidance for all three vaccine strains after receiving 2 doses of vaccine. Immune responses to the B strain were weaker relative to H1 and H3 strains, especially in children 6 months to 3 years of age, but the responses exceeded pre-specified endpoint criteria. Furthermore, B-strain immune responses have historically been weaker than H1 and H3 strains.

Children enrolled in this study appeared to have reasonable safety responses to this vaccine based on both expected and unexpected safety events. The safety database for children and adolescents consists primarily of data from CSLCT-FLU-04-05. Children enrolled in this study were followed for 180 days after each dose for expected and unexpected adverse reactions. Injection site pain and erythema were the most common adverse events following vaccination. Younger children appeared to experience slight higher fever and influenza-like symptoms than older children. Two SAEs possibly related to vaccination were reported: both were occurrences of fever and vomiting following a booster dose of vaccine. There were no deaths or discontinuations due to AEs. No unusual new trends or safety signals were identified in the pediatric study CSLCT-FLU-04-05, in the interim Annual Report from a pediatric safety Post-Marketing Commitment (PMC), or in post-marketing surveillance from November 2002 to April 30, 2009.

Overall, the data provided in the Prior Approval BLA Supplement, BLA 125254 amendment 132 suggests that Afluria is safe and efficacious (based on immune response) in children 6 months to < 9 years of age. Additionally, based on this sponsor provided adverse event and immune response data collected within study CSLCT-FLU-04-05, Afluria appears to have a favorable risk benefit ratio in children. Assuming immunogenicity and safety data can reasonably be extrapolated from the 3 to < 9 year old children examined in study CSLCT-FLU-04-05 and the adults previously examined in the original Afluria BLA submission, children 9 to < 18 years of age receiving Afluria should also have acceptable safety and efficacy response.

1.1 Conclusions and Recommendations

Based on the strength of the immunogenicity endpoint data and an acceptable safety profile provided within BLA 125254 amendment 132, the clinical review team including the reviewing

statistician recommends that Afluria be considered for accelerated approval in children 6 months to < 18 years of age because of potential clinical benefits that outweigh known risks. Post-marketing pediatric safety and non-inferiority studies are already in progress, will enhance the safety database, and will further support the efficacy data in this population; however based on the pediatric study CSLCT-FLU-04-05 provided in this submission, this vaccine appears to be relatively safe and efficacious.

1.2 Brief Overview of Clinical Studies

The submission in BLA 125254 amendment 132 included study results of one unblinded, uncontrolled pediatric study entitled CSLCT-FLU-04-05. The components of this BLA contained within this submission included:

- Module 1 Volume 1: Administrative information, labeling
- Module 2 Volume 1: Clinical Summary of Safety and Efficacy
- Module 5 Volumes 1-5: Complete Study Reports for CSLCT-FLU-04-05 the pivotal pediatric open label Primary Vaccination and Booster Dose studies; Case Report Forms, SAE Report Forms, Post-Marketing Reports, and literature.

The clinical study examined approximately 300 healthy male and female children (150 Children ≥ 6 months to < 3 years of age and 150 Children ≥ 3 years to < 9 years of age) in the open label unblinded study to determine the safety and efficacy of Afluria (CSLs unadjuvanted seasonal trivalent flu vaccine) in children 3 months to 9 years of age. Children enrolled in this study were administered two doses of Afluria vaccine. Table 1) provides a brief description of the study provided within the submission.

Table 1) Summary of Study Examined in BLA

Study/ Date	Age group	N**	US IND/ Sites	Dose	Phase	Design
CSLCT-FLU-04-05 Mar-Jul 2005 (both PAS and BLA)*	≥6mos <3yr ≥3yr to<9yr	151 147	No / Australia	Two doses 30 days apart	III	Open label Unblinded Uncontrolled

The primary objective of this study was to evaluate the safety of CSL IVV in a pediatric population (≥ 6 months to < 3 years and ≥ 3 years to < 9 years) through the assessment of:

- Local and systemic solicited AEs for 7 days post each vaccination;
- Unsolicited Adverse Events for 30 days post each vaccination;
- Serious Adverse Events for 6 months after the last primary vaccination.

The secondary objective was to evaluate the immunogenicity of all three influenza strains included in the CSL IVV in a pediatric population (≥6 months to < 3 years and ≥ 3 years to < 9 years) after the second administered dose. The primary criteria for establishing efficacy were considered consistent with the recommendations for adults in the FDA Guidance for Industry:

Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines: May 2007

- The lower bound of the two-sided 95% CI for the percent of subjects achieving a four-fold increase in HI antibody titer to a minimum of 1:40 (seroconversion rate) should meet or exceed 40%.
- The lower bound of the two-sided 95% CI for the percent of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 70%.

For the three strains included in CSLs Afluria:

- 15µg A/New Caledonia/20/99 (IVR-116) (A/New Caledonea/20/99 (H1N1)-like)
- 15µg A/Wellington/1/2004 (IVR-139) (A/Wellington/1/2004 (H3N2)-like)
- 15 µg B/Jiangsu/10/2003 (B/Shanghai/361/2002-like).

1.3 Major Statistical Issues and Findings

This BLA provided the results of an unblinded open label study that administered Afluria to pediatric subjects in Australia. Ideally, a study should be blinded, well-controlled, and be powered to illustrate safety and efficacy. Due to constraints related to the influenza shortage in 2004 and current concerns related to the circulating H1N1 pandemic swine flu strain, less stringent criteria for submission for BLA is acceptable.

While this study is small (<300 subjects), unblinded, and lacks a comparator treatment arm, analysis of the efficacy, immunogenicity, and safety response data appear to be adequate to support approval. The immune response data of both seroprotection and seroconversion show sufficient response to meet the criteria based on the FDA Guidance for licensing Seasonal Influenza Vaccines (for Adults—there is no pediatric guidance as of Oct 2009) for all strains. Additionally, the adverse events reported within this study are consistent with other flu products. The most commonly occurring adverse events include injection site pain and erythema, which were resolved quickly (within 1-7 days).

2. INTRODUCTION

2.1 Overview

On September 28, 2009 CSL's trivalent seasonal influenza vaccine Afluria was approved for Adults 18 years of age or older. Subsequently, the influenza vaccine Afluria has been studied in the pediatric population. This submission includes the results of a pediatric study that was performed as a part of the post marketing commitment for this influenza vaccine product.

Study CSLCT-FLU-04-05 examined the safety and immunogenicity of Afluria in a pediatric population. This pediatric study was unblinded, open-label, single treatment arm study. The primary responses of interest were the safety and immune response of Afluria in children 6 months to 3 years of age and children 3 years to 9 years of age.

The sample size of 300 was based on standards set by the Swedish Medical Products Agency specific to safety studies of influenza vaccine in pediatric populations. No inferential statistics were used. Statistical analyses for both immunogenicity and safety results comprised summary and descriptive statistics

Due to the small sample size and lack of comparator arm, this study was not designed or powered to perform any statistical tests. However, utilizing the data, including immunogenicity and safety responses, descriptive statistics were computed and presented.

2.2 Data Sources

Data sources include the paper copy of CSLs provided study reports and data sets. The datasets including subject immune responses, AEs, demographics, etc., were located within the CBER EDR:

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3. STATISTICAL EVALUATION

In addition to the pediatric study in Australia, the sponsor provided in this submission supportive evidence including positive results of studies examining efficacy, immunogenicity, and safety responses of Afluria in adult populations of subjects 18 years of age and older.

This statistical review will focus on analysis, results, and conclusions from the pediatric study: CSLCT-FLU-04-05.

3.1 Evaluation of Immunogenicity

Design Overview

This was a Phase III, open-label, non-randomized, non-blinded trial conducted at two sites in Australia in support of European licensure for a pediatric indication. A sample size of 300 was planned as specified by the Swedish Medical Products Agency (MPA). Subjects were to be assigned to Group A (150 subjects, ≥ 6 months to < 3 years) or Group B (150 subjects, ≥ 3 years to < 9 years). Once enrolled, participants were to receive 2 doses of vaccine 30 days apart (+/- 3 days): Group A 0.25 mL and Group B 0.5 mL. A booster dose was to be administered 12 months after the primary vaccination series; however, the BLA is proposed to examine the immunogenicity of the initial 2 doses. The "booster" dose given after 1 year was only considered as providing supplementary information about expected and unexpected adverse events.

Study Timing

- Day 0, Vaccination Dose 1, Visit 1: informed consent, medical history including previous influenza illness, targeted exam, pre-vaccination anti-HI antibody titers, vaccination, post-vaccination observation for 30 minutes.
- Day 0-7: 7 day Solicited AE diary card and 30 day post-vaccination Unsolicited AE diary card.
- Day 10 ± 2: review of diary cards.
- Day 30 ± 3, Vaccination Dose 2, Visit 2: return 30 day Unsolicited AE diary card, assessment of AEs, SAEs, interval history and medical evaluation, and post-vaccination anti-HI antibody titers prior to Vaccination Dose 2. 30 minute post-vaccination observation for anaphylactic reactions. Dose Two 7 and 30 day diary cards issued for solicited and unsolicited AEs respectively.
- Day 60 ± 3, Primary Vaccination Exit Evaluation: 7 and 30 day diary cards returned, all AEs and SAEs assessed, followed until resolution/stabilization. Brief medical evaluation, post-vaccination anti-HI antibody titers.
- Intercurrent Flu-like Illness Visit: for symptoms occurring at any time between the first dose of Study Vaccine and the Primary Exit Evaluation. Attempt at viral isolation from a throat swab within four days of onset of symptoms.
    - Criteria for ILI: axillary temperature of ≥37.5ºC or oral temperature ≥38.0ºC, and at least one flu-like symptom (headache, cough, sore throat, rhinitis, wheezing/shortness of breath, myalgia, earache, vomiting/diarrhea, anorexia, and irritability).

A summary of the data collection during study CSLCT-FLU-04-0 can be observed in the following table provided by the sponsor within the submission.

Table 2) Schedule of Procedures and Assessments Study CSLCT-FLU-04-05

Assessments	Pre-Study	Day 0 Dose 1	Day 10 ± 2	Day 30 ± 3 Dose 2	Day 60 ± 3 Primary Vaccination Exit	Day 365 ± 14 Booster Dose	30 ± 3 days after Booster Vaccination Booster Vaccination Exit
Invitation to Participate	✓						
Informed Consent		✓					
Medical History (including Influenza History)		✓				✓	
Brief Medical Examination		✓		✓	✓	✓	✓
Axillary/Oral Temperature*		✓		✓		✓	
Review of Inclusion/Exclusion Criteria		✓					
Review Ongoing Eligibility				✓		✓	
Blood Sample - Immunogenicity Assessments		✓		✓	✓	✓	✓
Vaccination		✓		✓		✓	
Provision of Study Supplies and Instructions.		✓		✓		✓	
7-Day Diary Card Review		✓		✓		✓	
30-Day Diary Card Review		✓		✓		✓	
7-Day Diary Card Collection			✓		✓		✓
30-Day Diary Card Collection				✓	✓		✓
Telephone contact (if 7-Day Diary Card has not been returned)			✓				
Review of Concomitant Medications		✓		✓	✓	✓	✓
Assessment & Documentation of Adverse Events (AEs)		✓	✓	✓	✓	✓	✓
Assessment of flu-l ke Illness (including throat swabs if applicable)		✓ Participants may have attended additional visits for medical confirmation of flu-l ke symptoms at any time between Days 0 and 60 ± 3				✓ Participants may attend additional visits for medical confirmation of flu-like symptoms at any time between day 365 ± 14 and the Booster Vaccination Exit Visit.	
Assessment & Documentation of Serious Adverse Events (SAEs)		✓ SAEs to be reviewed and documented up to 6 months after Second Primary Vaccination (Day 30 ± 3)				✓ SAEs to be reviewed and documented up to 6 months after Booster Vaccination	

Source: Table 8.1 within sponsor provided BLA submission, Module 5 Vol 1 Sect 5.2.5.2 p16

Study Population

In this study, a sample size of 300 was planned based on standards set by the Swedish Medical Products Agency specific to safety studies of influenza vaccine in pediatric populations.

- Group A (150 subjects, ≥ 6 months to < 3 years)
- Group B (150 subjects, ≥ 3 years to < 9 years).

Inclusion/Exclusion Criteria

In this study inclusion and exclusion criteria were prespecified. Key inclusion criteria included:

- Healthy male or female children, aged ≥6 months to <9 years at the time of the first study vaccination
- Parent(s) or Guardian(s) provide written informed consent to participate in the study
- Able to provide a pre-vaccination sample of up to 5 mL of venous blood without undue distress/discomfort, and
- Born after a normal gestation period (between 36 and 42 weeks).

Key exclusion criteria included allergies to eggs, previous influenza vaccine, health issues, history of Guillain-Barré Syndrome, major congenital defect or serious illness, history of neurologic disorders or participation in other clinical trials. An exhaustive list of the exclusion criteria can be found within the clinical review.

Study Design and Endpoints

Endpoints

Primary endpoints were related to the safety assessment and were evaluated on all participants who received at least one dose of Study Vaccine (the Safety Population).

- Solicited local and systemic AEs
- Local solicited AEs included: pain, redness, and swelling
- Systemic solicited AEs included: fever, headache, cough, sore throat, rhinitis, wheezing, myalgia, ear ache, vomiting/diarrhea, loss of appetite, and irritability
- Unsolicited AEs
- SAEs

Secondary endpoints related to immunogenicity and were assessed on all participants who received at least one dose of the Study Vaccine consistent with the prescribed dose for their age group and who had an evaluable pre-vaccination and at least one post-vaccination anti-HI antibody titer (Evaluable Population).

Pre- and post-vaccination anti-HI antibody titers were collected and evaluated according to the CPMP/BWP/214/96 guidance document which requires that at least one of the following criteria be met by each of the three vaccine strains:

- Proportion with a four-fold increase in HI antibody titer to a minimum of 1:40 should be > 40%;
- Mean geometric increase in HI antibody titer should by > 2.5 fold;
- Proportion of participants achieving a post-vaccination HI antibody titer of ≥ 1:40 should be > 70%.

The three strains examined in the pediatric influenza vaccine study CSLCT-FLU-04-05 to examine CSL Afluria included:

- 15µg A/New Caledonia/20/99 (IVR-116) (A/New Caledonea/20/99 (H1N1)-like)
- 15µg A/Wellington/1/2004 (IVR-139) (A/Wellington/1/2004 (H3N2)-like)
- 15 µg B/Jiangsu/10/2003 (B/Shanghai/361/2002-like).

For simplicity in this review, these strains will be denoted by: H1N1, H3H2, and B strain.

Patient Disposition, Demographic and Baseline Characteristics

The study enrolled 298 pediatric subjects with 151 subjects in Group A ≥ 6 months to < 3 years of age and 147 subjects in Group B ≥ 3 years to < 9 years of age. Of the 298 subjects enrolled, 293 subjects completed the study; however, only 271 received both doses of vaccine.

Table 3) Participant Disposition Study CSLCT-FLU-04-05

	Group A ≥6mos to <3yrs		Group B ≥3yrs to <9yrs		Total	
	n	(%)	n	(%)	n	(%)
Total enrolled	151	(100)	147	(100)	298	(100)
Vaccinated Dose 1	151	(100)	147	(100)	298	(100)
Vaccinated Dose 2	148	(98.0)	145	(98.6)	293	(98.3)
Safety population (Received Dose 1)	151	(100)	147	(100)	298	(100)
Evaluable population						
Received Dose 1	143	(94.7)	144	(98.0)	287	(96.3)
Received Dose 1 + 2	139	(92.1)	132	(89.8)	271	(98.6)
Protocol completed	148	(98.0)	145	(98.6)	293	(98.3)
Protocol withdrawals	3	(2.0)	2	(1.4)	5	(1.7)
Reason for withdrawal						
Death	0		0		0	
SAE	0		0		0	
AE	0		0		0	
Protocol violation	0		0		0	
Withdrew consent	2	(1.3)	2	(1.4)	4	(1.3)
Moved away	0		0		0	
Lost to follow-up	1	(0.7)	0		1	(0.3)
Other	0		0		0	
Protocol violation	0		0		0	

The study enrolled only Caucasian individuals (justified by the lack of ethnic diversity in the region of Australia that the study was conducted). Within the study, 140 subjects were male and 158 subjects were female.

Statistical Methodologies

The sample size of 300 was based on standards set by the Swedish Medical Products Agency specific to safety studies of influenza vaccine in pediatric populations. No inferential statistics were used. Statistical analyses for both immunogenicity and safety results included only summary and descriptive statistics.

The Patient Populations are as follows:

> **Safety**: all participants who received at least one dose of study vaccine consistent with the prescribed dose for their age group.
>
> **Evaluable**: all participants who received at least one dose of the Study Vaccine consistent with the prescribed dose for their age group and who had an evaluable pre-vaccination and at least one post-vaccination anti-HI antibody titer; did not experience a confirmed ILI during the study; and did not meet elimination criteria.

The **Immunogenicity evaluations** within the study included the following statistics calculated for each vaccine strain and using the results of the anti-HI antibody titers:

- Seronegative: Number and percentage of evaluable participants with pre-vaccination serum HI titre <10 pre-vaccination.
- Geometric mean of pre-vaccination serum HI titres and 95% confidence interval.
- Pre-vaccination seroprotection rate: Number and percentage of evaluable participants with pre-vaccination serum HI titres ≥40, and 95% binomial confidence interval.
- Geometric mean of post-vaccination serum HI titres and 95% confidence interval.
- Seroconversion rate: Number and percentage of evaluable participants with serum HI titre <10 pre-vaccination (undetectable) and an increase in serum HI titre to ≥40 post-vaccination.
- Significant increase: Number and percentage of evaluable participants with serum HI titre ≥10 pre-vaccination and at least a four-fold antibody titre increase post-vaccination.

The **Safety evaluations** within the study included the following information:

- The number and percentage of Solicited AEs for each age group for 7 days following Dose 1 (Day 0), Dose 2 (Day 30), and Booster vaccination (Day 365).
- Severity and relationship to the Study Vaccine. (Note: Those reported without a severity grading were assumed to be Grade 3 and documented in a footnote. The sponsor assumed that the first occurrence of all solicited local AEs was related to the Study Vaccine).
- The number and percentage of Unsolicited AEs for the Primary Vaccine series was recorded for each age cohort, according to MedDRA system organ class and preferred

term, severity, and causality. Unsolicited AEs were collected for 30 days following Dose 1, Dose 2, and the Booster vaccinations.

- SAEs were reviewed and documented for up to 6 months after Dose 2 and again after the Booster vaccination.

Changes in the Conduct of the Study or Planned Analyses

The protocol stated that all local AEs were to be considered related to the Study Vaccine. A change was made to the protocol such that the investigator was to determine the relationship to the Study Vaccine of local AEs which recurred after initial resolution.

The analysis of unsolicited AEs planned in the SAP did not consider the periods following each dose separately. Each of the planned unsolicited AE tables was generated following each dose. This change occurred after the database lock.

These changes did not affect the outcome or conclusions of the study.

Results and Conclusions

In this study, 298 subjects were enrolled into the single treatment arm of CSL's trivalent seasonal influenza vaccine: Afluria. Of the 298 subjects enrolled, there were 151 subjects in Group A $\geq$ 6 months to < 3 years of age and there were 147 subjects in Group B $\geq$ 3 years to < 9 years of age. The vaccine administration of the two doses of the Afluria vaccine was 30 ± 3 days apart. For the first 7 days following administration of vaccine, the subjects expected and unexpected Adverse Events were to be collected. Additionally 30 days following each vaccine administration blood was to be drawn and analyzed for immune response.

The results of this study demonstrate acceptable immunogenicity response to the Afluria vaccine in pediatric population. In particular, the primary immunogenicity response of seroconversion and seroprotection were met for all 3 influenza strains. In the table below, Table 4) the reviewing statistician provides her results of the primary immunogenicity responses for both age groups and all three influenza strains. It is of interest to note that these results reflect analysis performed on the "Full Analysis" study population including all subjects receiving at least one dose of Afluria. These results are very similar to the sponsor's results from the "per protocol" analysis and provide reassurance that this product appears to provide sufficient immune response based on FDA recommendations.

Table 4) Immunogenicity Endpoints – Study CSLCT-FLU-04-05 – Statistical Analysis of the Primary Vaccination for All Treated Subjects who received at least one dose of Afluria (Agency Statistician)

Strain/ Endpoint	FDA criteria	Group A ≥6mos to <3yrs		Group B ≥3yrs to <9yrs	
		LB 95% CI		LB 95% CI	
	Lower bound 95% CI		**Dose 2 n=149**		**Dose 2 n=147**
H1N1					
% 4-fold increase *	>40%		**88.4%**		**84.2%**
% with HI ≥ 1:40**	>70%		**89.1%**		**85.5%**
H3N2					
%4-fold increase	>40%		**84.3%**		**63.0%**
% with HI ≥1:40	>70%		**93.2%**		**89.6%**
B Strain					
% 4-fold increase	>40%		**90.6%**		**86.2%**
% with HI ≥ 1:40	>70%		**90.5%**		**86.9%**

*% 4-fold increase refers to the proportion of subjects with a four-fold increase in HI titer to a minimum of 1:40.
** % with HI ≥1:40 refers to the proportion with a post-vaccination HI titer of ≥1:40.

For all three influenza strains included in the vaccine (H1N1, H3N2, and B-strain) and both age groups, subjects met the immunogenicity response criteria to ensure adequate seroprotection and seroconversion. Thus, it appears this product meets criteria for efficacy based on immune response and is sufficient to support approval of this influenza vaccine: Afluria.

3.2 Evaluation of Safety

Historically, inactivated seasonal trivalent influenza vaccine is typically considered very safe with minimal adverse events. Expected adverse events are commonly injection site pain and erythema. This study illustrated that this product appears reasonably safe and is comparable to other seasonal influenza vaccines in the number and severity of expected side effects. The medical officer has a detailed description of the safety events. However, for completeness two tables, Table 5) and Table 6), are provided, which illustrate the percent of subjects experiencing different grade AEs as well as the percent of subjects experiencing solicited AEs.

Table 5) Solicited AEs by Severity Grade – CSLCT-FLU-04-05 (After Dose 2)

	Group A n=151 ≥6 mos to < 3 years				Group B n=147 ≥3 years to <9 years			
Event	Grade 1 %*	Grade 2 %	Grade 3 %	Total	Grade 1 %	Grade 2 %	Grade 3 %	Total
Local AEs								
Pain	25.2	11.9	0	37.1	42.2	17.7	2.0	61.9
Redness	31.1	6.6	0	37.7	26.5	12.2	6.8	45.6
Swelling	17.2	3.3	0	20.5	17.0	8.2	2.0	27.2
Systemic AEs								
Fever	15.2	6.6	0.7	22.5	7.5	0.7	0	8.2
Headache	2.0	0.7	0.7	3.3	8.8	1.4	0.7	10.9
Cough	23.8	6.6	1.3	31.8	17.7	1.4	0.7	19.0
Sore throat	2.7	1.3	1.3	5.3	8.2	2.0	0.7	10.9
Rhinitis	37.1	9.3	1.3	47.7	25.9	2.7	0	28.6
Wheezing	6.6	2.0	0	8.6	1.4	0.7	0	2.0
Myalgia	2.0	0.7	0	2.7	6.1	2.0	0	8.2
Earache	2.0	1.3	0	3.4	0.7	0.7	0	1.4
Vomiting/ Diarrhea	9.3	2.0	2.6	13.9	6.1	0.7	0	6.8
Loss of Appetite	15.9	5.3	2.6	23.8	4.8	0.7	0	5.4
Irritability	24.5	11.9	4.6	41.1	15.0	2.0	0	17.0

*For any given AE, the denominator for the % is the # of subjects in the Safety Population minus the # of subjects who were not assessed for that AE.

Table 6) Summary of Solicited AEs CSLCT-FLU-04-05

	Group A, n=151 ≥6 mos to <3 years	**Group B, n=147 ≥3 years to <9 years**
Event	Dose 2	Dose 2
Local AEs	53.6	70.1
Pain	37.1	61.9
Erythema	37.7	45.6
Swelling	20.5	27.2
Systemic AEs	70.7	55.1
Irritability	41.1	17.0
Rhinitis	47.7	28.6
Fever	22.5	8.2
Cough	31.8	19.0
Loss of appetite	23.8	5.4
Vomiting/diarrhea	13.9	6.8
Headache	3.3	10.9
Myalgia	2.7	8.2
Sore throat	5.3	10.9
Wheezing/shortness of breath	**8.6**	2.0
Earache	3.4	1.4

3.3 Gender, Race, Age and Other Special/Subgroup Populations

CSL Study CSLCT-FLU-04-05 was performed in Australia in March-July (Australian Winter) in 2005. Infants and toddlers were administered Afluria in an unblinded open label study. Only Caucasian subjects enrolled in the study. Further demographics of the enrolled subjects can be found in the table below.

Table 7) Demographics and Baseline Characteristics CSLCT-FLU-04-05

Characteristic	Descriptive Statistic	Group A ≥6 mos to <3 years n=151	Group B ≥3 years to < 9 years n=147
Age (years)	Mean (SD) Median Minimum Maximum	1.7 (0.43) 1.9 0.5 2.0	5.0 (1.73) 5.0 3.0 8.0
Gender	Male N (%) Female N (%)	74 (49.0%) 77 (51.0%)	66 (44.9%) 81 (55.1%)
Prior influenza illness	Yes N (%) No N (%)	19 (12.6%) 132 (87.4%)	15 (10.2%) 132(89.8%)
Prior Influenza Vaccination	Yes N (%) No N (%)	0 151 (100%)	0 147 (100%)

Since this study included only Caucasian subjects, subset analysis stratified by race is impossible. Also, the limited age enrollment precludes meaningful subgroup analyses by age categories. However, there were males and females enrolled in this study in similar proportions in the 6 month to 3 year age group. In the 3 year to 9 year age group there were slightly more females enrolled than males. Analysis of the immunogenicity endpoints yield similar results and conclusions regardless of gender as illustrated in the table below, Table 8), which verifies the immunogenicity of this product based on both seroconversion and seroprotection regardless of gender.

Table 8) Efficacy Response Stratified by Gender and Age Group

Strain/ Endpoint	**FDA criteria**	**Group A ≥6mos to <3yrs**		**Group B ≥3yrs to <9yrs**	
		N=149		N=147	
	Lower bound 95% CI	**Males n= 73**	**Females n= 76**	**Males n= 66**	**Females n= 81**
H1N1					
% 4-fold increase *	>40%	91.5%	86.6%	80.0%	89.9%
% with HI ≥ 1:40**	>70%	91.6%	85.3%	80.0%	87.4%
H3N2					
%4-fold increase	>40%	95.8%	90.6%	84.6%	93.6%
% with HI ≥1:40	>70%	84.7%	83.5%	58.7%	66.3%
B Strain					
% 4-fold increase	>40%	92.7%	87.9%	84.6%	88.7%
% with HI ≥ 1:40	>70%	92.7%	87.9%	84.6%	87.9%

Comparable response for males and female subjects were observed when examining the immunogenicity endpoints of seroconversion and seroprotection.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

This study was not designed to test any hypothesis. The study was a single arm, unblinded, open label study to examine the safety and immune response of Afluria in a pediatric population of subjects 6 months to 9 years of age. Safety and immune response data was to be collected including: expected and unexpected Adverse Events as well as Immune response to the three influenza strains included in the Afluria vaccine.

The data suggests that this trivalent seasonal influenza vaccine has a reasonable safety profile with comparable trends of adverse events to other seasonal influenza vaccines. Additionally, the trends observed within this study provide supportive evidence that Afluria provides adequate immune response based on the FDA Guidance for Influenza Vaccines. While this guidance is written specifically for adult populations, using identical criteria this vaccine, Afluria, provides adequate immune response for all three influenza strains included in this product.

The sponsor's written assessment of the pediatric Afluria study, CSLCT-FLU-04-05 included in this BLA submission demonstrates that the Afluria vaccine has a reasonable risk benefit profile. Furthermore, analysis performed by the Agency statistician of select primary endpoints of safety and immune response data collected within this submission support the sponsor's assertion that this product has an acceptable safety and efficacy (based on immune response) profile.

4.2 Conclusions and Recommendations

Based on the strength of the immunogenicity endpoint data and an acceptable safety profile provided within BLA 125254 amendment 132, the clinical review team including the reviewing statistician recommends that Afluria be considered for accelerated approval in children 6 months to < 18 years of age because of potential clinical benefits that outweigh known risks. Post-marketing pediatric safety and non-inferiority studies, already in progress, will enhance the safety database and will further support the efficacy data in this population; however based on the pediatric study CSLCT-FLU-04-05 provided in this submission, this vaccine appears to be relatively safe and efficacious.