

**Public Assessment Report  
for paediatric studies submitted in accordance  
with Article 46 of Regulation (EC) No1901/2006, as  
amended**

**Afluria/Enzira  
Influenza vaccine**

**SE/W/013/pdWS/001**

**Marketing Authorisation Holder:  
CSL Biotherapies**

<b>Rapporteur:</b>	Sweden
<b>Finalisation procedure (day 120):</b>	28 April 2011
<b>Date of PAR</b>	14 June 2011

## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Afluria/Enzira
INN (or common name) of the active substance(s):	Influenza Vaccine
MAH:	CSL Biotherapies GMBH
Currently approved Indication(s)	Prophylaxis of influenza, especially in those who run an increased risk of associated complications.  The use of Afluria should be based on official recommendations.
Pharmaco-therapeutic group (ATC Code):	J07B B02
Pharmaceutical form(s) and strength(s):	Suspension for injection in a pre-filled syringe.

## **I. EXECUTIVE SUMMARY**

No SmPC and PL changes are proposed.

## **II. RECOMMENDATION**

No further regulatory action is required.

## **III. INTRODUCTION**

On November 18, 2010 the MAH submitted completed paediatric studies for Afluria/Enzira, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Afluria/Enzira and that there is no consequential regulatory action.

## **IV. SCIENTIFIC DISCUSSION**

### **IV.1 Information on the pharmaceutical formulation used in the study(ies)**

The formulation used in the clinical trials is the same as the approved formulation.

### **IV.2 Clinical aspects**

#### **1. Introduction**

The MAH submitted final reports for:

- CSLCT-USF-06-29
- CSLCT-USF-07-36
- CSLCT-CHF-06-25
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#### **2. Clinical studies**

**CSLCT-USF-06-29:** A Phase IV, Open-Label, Multi-Center Study to Evaluate the Safety and Tolerability of CSL Limited's Influenza Virus Vaccine in a Pediatric Population Aged  $\geq 6$  Months to  $< 18$  Years

#### **➤ Description**

This prospective, open-label study was conducted in 1992 participants aged 6 months to less than 18 years at seven study sites in Australia. The study was conducted during the 2009 Southern Hemisphere autumn.

#### **➤ Methods**

- **Objective(s)**

The primary objective was to evaluate the safety and tolerability of CSL Limited's Influenza Virus Vaccine (CSL's IVV) in a pediatric population aged 6 months to less than 18 years. The safety and tolerability of the product were determined by the frequency, severity and duration of:

- Solicited adverse events (AEs) for 6 days (total 7 days) following any study vaccination in each age cohort;
- Unsolicited AEs for 29 days (total 30 days) following any study vaccination in each age cohort;
- Serious adverse events (SAEs) for 180 days following any study vaccination in each age cohort; and
- New onset of chronic illness (NOCI) for 180 days following any study vaccination in each age cohort

- **Study design**

- Study population /Sample size

Healthy children were eligible for enrollment if they were aged 6 months to less than 18 years and were born at or after 36 weeks gestation (this criterion applied only to participants aged younger than 9 years) or returned a negative pregnancy test (this criterion applied only to female participants aged 9 years or older).

The main exclusion criteria were: an allergy to any vaccine components; evidence of an active infection; receipt of an experimental or seasonal influenza vaccine in the previous 6 months; a confirmed or suspected immunosuppressive condition; a history of Guillain-Barré Syndrome; a major congenital defect or serious illness; a history of neurologic disorders or seizures; administration of immunoglobulins or any blood products; participation in a clinical study or use of an investigational compound; immunosuppressive or immunomodulatory medication, including systemic corticosteroids; and treatment with cytotoxic drugs.

With a planned Safety Population of 2025 participants, AEs with population rates of 1 in 1000 had an 86.8% probability of being detected. Adverse events with population rates of 1 in 676 had a 95% chance of being observed with 2025 participants. Within a single stratum of 810 participants, AEs with population rates of 1 in 300 had a 93.3% chance of detection and AEs with population rates of 1 in 271 had a 95% chance of detection. For the single stratum of 405 participants, AEs with population rates of 1 in 136 had a 95% chance of detection.

1992 participants were enrolled into the study and stratified by age into three cohorts:

- Cohort A (aged 6 months to less than 3 years), 710 participants;
- Cohort B (aged 3 to less than 9 years), 880 participants;
- Cohort C (aged 9 to less than 18 years), 402 participants

- **Treatments**

The 2009 Southern Hemisphere formulation of CSL's IVV was supplied as a thimerosal-free aqueous suspension in pre-filled syringes. The two doses of CSL's IVV differed in injection volume and antigen content. Each 0.25 mL dose contained 7.5 mcg HA antigen for each of the three strains recommended by the World Health Organization for the 2009 Southern Hemisphere influenza season. Each 0.5 mL dose contained 15 mcg HA antigen for each of the three recommended strains. Two half doses (0.25mL) doses were given to previously unvaccinated children 6 months to <3 years of age. Two full doses (0.5 mL) were given to previously vaccinated children 3-9 years of age. Previously influenza vaccinated children only received a single full or half dose respectively. Children 9-18 years of age were given a single full dose.

- **Outcomes/endpoints**

The safety and tolerability of CSL's IVV were determined by the frequency, severity and duration of:

- Solicited AEs for 6 days (total 7 days) following any study vaccination in each age cohort;
- Unsolicited AEs for 29 days (total 30 days) following any study vaccination in each age cohort

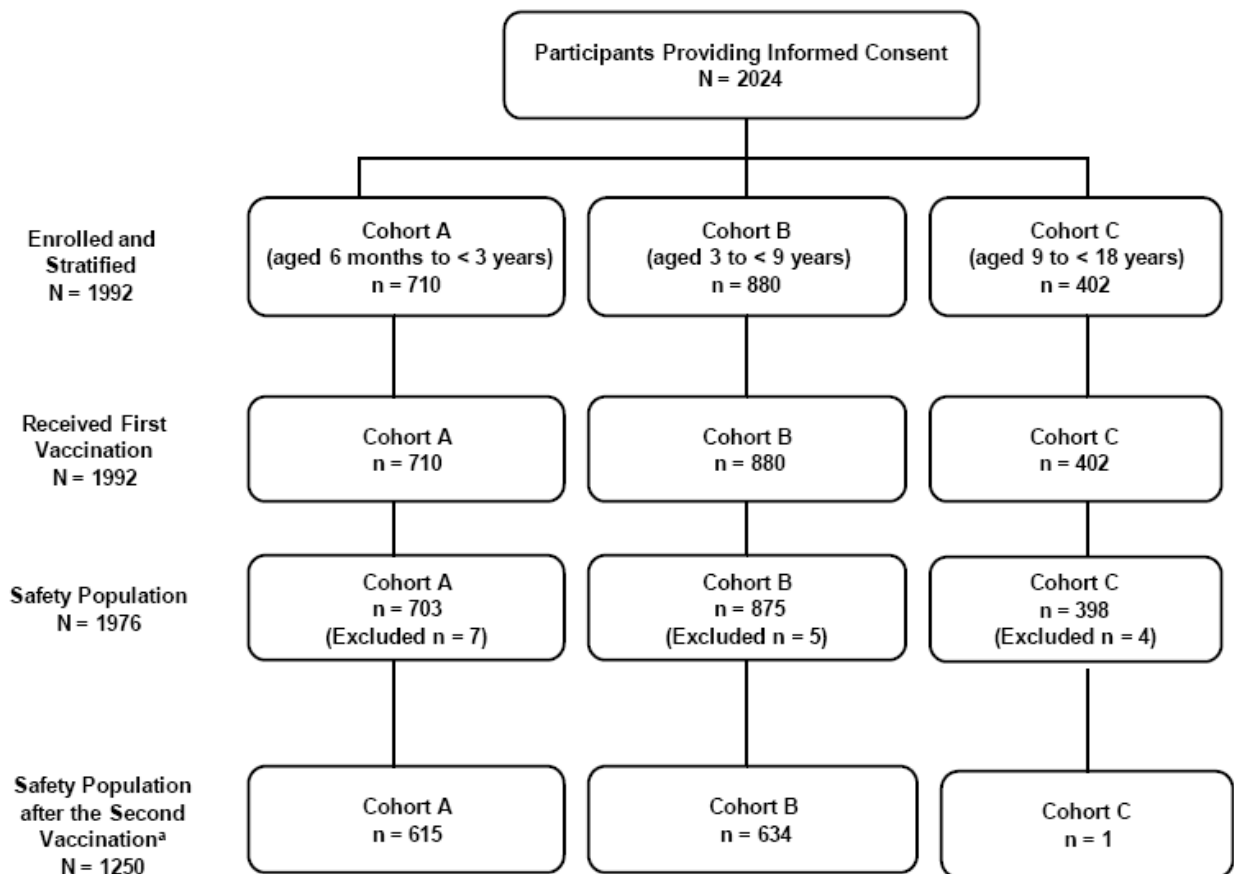
- NOCIs for 180 days following any study vaccination in each age cohort
- Statistical Methods

➤ **Results**

- Recruitment/ Number analysed

The disposition of the study subjects is summarized in Figure 10.1 below.

Figure 10.1 Participant Disposition



<sup>a</sup> Two participants in Cohort B and one participant in Cohort C received the second vaccination in error and provided safety follow-up data.

- Efficacy results  
Not applicable.
- Safety results

There were no deaths and no vaccine-related SAEs reported during the study (Table 2). Enrollment halting rules were not triggered. A total of 17 participants reported 20 NOCIs, of which two (food allergy and eczema) were considered by the Investigator to be possibly related to CSL’s IVV. No participants were withdrawn because of an SAE. Though 17 participants were listed as withdrawn because of an AE, review of the study data revealed that these participants were erroneously listed as having withdrawn from the

study. Rather, these 17 participants should have been listed as having completed the study because they did provide the 180-day follow-up safety data. Therefore, no participant discontinued from the study because of an AE.

**Table 2 Summary of AEs Reported after the First or Second Vaccination (Safety Population)**

Adverse Event	Cohort A	Cohort B	Cohort C	Total
	N = 703 n (%)	N = 875 n (%)	N = 398 n (%)	N = 1976 n (%)
One or more AEs	643 (91.5)	767 (87.7)	337 (84.7)	1747 (88.4)
Withdrawal due to an AE	10 (1.4)	7 (0.8)	0	17 (0.9)
Solicited AEs				
Any solicited local AEs	305 (43.4)	585 (66.9)	281 (70.6)	1171 (59.3)
Any solicited systemic AEs	504 (71.7)	408 (46.6)	170 (42.7)	1082 (54.8)
Unsolicited AEs <sup>a</sup>	531 (75.5)	521 (59.5)	167 (42.0)	1219 (61.7)
Unsolicited AEs considered related to CSL's IVV <sup>b</sup>	153 (21.8)	153 (17.5)	36 (9.0)	342 (17.3)
Deaths	0	0	0	0
SAEs	19 (2.7)	5 (0.6)	2 (0.5)	26 (1.3)
SAEs considered related to CSL's IVV <sup>b</sup>	0	0	0	0
Withdrawal due to a SAE	0	0	0	0
NOCIs	10 (1.4)	5 (0.6)	2 (0.5)	17 (0.9)
NOCIs considered related to CSL's IVV <sup>b</sup>	2 (0.3)	0	0	2 (0.1)

Abbreviations: AEs, adverse events; CSL's IVV, CSL's influenza virus vaccine; NOCIs, new onsets of chronic illness; SAEs, serious adverse events.

<sup>a</sup> Unsolicited AEs included unsolicited AEs from Day 0 to Day 29, and SAEs / NOCIs from Day 0 to Day 180 after the last vaccination.

<sup>b</sup> Related AEs were those assessed by the Investigator as having a causality of unknown, possibly, probably or definitely related to study vaccine.

### ***Solicited Local Adverse Events***

The frequency of solicited local AEs reported increased with age. Overall, fewer participants reported solicited local AEs after the second vaccination than after the first vaccination (Cohort A: 27.2% of participants; Cohort B: 49.2% of participants). In all cohorts, the most frequently reported solicited local AE was injection-site pain, followed by redness and swelling / lump. The majority of the solicited local AEs were of mild intensity and short lived.

### ***Solicited Systemic Adverse Events***

Solicited systemic AEs were reported by 60.3%, 39.5%, and 42.7% of participants in Cohorts A, B and C, respectively, after the first vaccination. Participants reported fewer solicited systemic AEs after the second vaccination than after the first vaccination (Cohort A: 42.4% of participants; Cohort B: 24.8% of participants). The most frequently reported solicited systemic AEs in Cohort A were irritability (52.3%), fever (38.3%) and loss of appetite (27.3%). The most frequently reported solicited systemic AEs in Cohort B were malaise (24.8%), fever (24.3%) and headache (17.9%). The most frequently reported solicited systemic AEs in Cohort C were headache (26.9%), myalgia (20.1%) and malaise (16.6%). In all cohorts, the majority of solicited systemic AEs were of mild or moderate intensity and short-lived.

Fever of severe intensity was reported by a small proportion of participants after the first vaccination (Cohort A: 13 participants; Cohort B: 7 participants), including 1 participant in Cohort A who experienced febrile convulsion on the day of vaccination. As per the protocol, the occurrence of fever greater than 40.0°C / 104°F (oral) or 39.5°C / 103.1°F (axillary) prohibited further vaccination. All 20 participants who experienced fever of severe intensity did not receive the second scheduled vaccination. All cases of severe

fever were treated with either ibuprofen or paracetamol. The severe intensity of the fever lasted less than 1.1 days.

### ***Unsolicited Adverse Events***

Unsolicited AEs after the first or second vaccination were reported by 61.7% of participants (Cohort A: 75.5% of participants; Cohort B: 59.5%; and Cohort C: 42.0%). The most frequently reported unsolicited AEs in all participants were upper respiratory tract infection, cough and rhinorrhea. The majority of participants reported these events as having a maximum intensity of mild or moderate.

### ***MAH's Conclusions:***

This Phase IV, open-label, multi-center study was designed to evaluate the safety and tolerability of CSL's IVV in pediatric participants aged 6 months to less than 18 years. Most AEs reported were expected solicited local or systemic reactions. Similarly, the nature and type of unsolicited AEs that were reported reflected the common conditions that can be expected in a pediatric population.

The majority of solicited AEs were mild or moderate in intensity and short-lived. In all cohorts, injection-site pain was the most frequently reported solicited local AE. The most frequent systemic AEs reported for Cohorts A, B and C, respectively were irritability, malaise and headache.

Of note, fever was reported by more participants in each of the younger cohorts than in Cohort C. Fever of severe intensity was reported by a small proportion of participants (Cohort A: 13 participants; Cohort B: 7 participants), including 1 participant in Cohort A who experienced a febrile convulsion on the day of vaccination. As per the protocol, these 20 participants did not receive a second vaccination. In all cases, the severe intensity of the fever lasted 1.1 days or less.

Overall, the AEs did not appear to affect the number of participants returning for second vaccination, as 96.0% of those eligible to receive two vaccinations did receive both vaccinations in this study.

The most commonly reported unsolicited AEs in all participants was upper respiratory tract infection. Other frequently reported unsolicited AEs were: teething, rhinorrhea, cough (Cohort A); cough, rhinorrhea and pyrexia (Cohort B); and headache, oropharyngeal pain and rhinorrhea (Cohort C). These events are representative of common illnesses typical of the pediatric population studied. There were no vaccine-related SAEs reported in this study, and only two of the reported NOCIs were considered related to study vaccine by the Investigators (food allergy and eczema).

In conclusion, CSL's IVV was generally well tolerated by the majority of participants aged 6 months to less than 18 years.

*Assessor's conclusions: The results are generally as can be expected, based on experience with other influenza vaccines.*

**CSLCT-USF-07-36:** A Phase III, Randomized, Observer-blind, Multi-center, Non-inferiority Comparison of the Immune Response of CSL Limited's Influenza Virus Vaccine Compared to a US licensed Trivalent Inactivated Split-Virion Influenza Vaccine in a Pediatric Population Aged  $\geq$  6 Months to  $<$  18 Years.

### ➤ **Description**

This prospective, randomized, observer-blind, multi-center, non-inferiority study was conducted in 1474 healthy children aged 6 months to less than 18 years at 23 sites in the US, during the Northern Hemisphere's 2009 autumn. The purpose of the study was to compare the immunogenicity of CSL's IVV (2009/2010 formulation) to Fluzone in healthy children. The safety and tolerability of CSL's IVV was also evaluated

### ➤ **Methods**

- Objective(s)

**Primary Objective:** To demonstrate that vaccination with CSL Limited's Influenza Virus Vaccine (CSL's IVV) elicits an immune response that is not inferior to that of a US licensed inactivated split-virion influenza vaccine (Fluzone®) in a pediatric population aged 6 months to less than 18 years.

**Secondary Objective:** To assess the safety and tolerability of CSL's IVV in a pediatric population aged 6 months to less than 18 years

- Study design

This study was a phase III prospective, randomized, observer-blind, multi-center, non-inferiority study.

- Study population /Sample size

Healthy children were eligible for enrollment if they were aged 6 months to less than 18 years and were born at or after 36 weeks gestation (this criterion applied only to participants aged younger than 9 years) or returned a negative pregnancy test (this criterion applied only to female participants aged 9 years or older).

The main exclusion criteria were: an allergy to any vaccine component; evidence of an active infection; receipt of an experimental or seasonal influenza vaccine in the previous 6 months; a confirmed or suspected immunosuppressive condition; a history of Guillain-Barré Syndrome; a major congenital defect or serious illness; a history of neurologic disorders or seizures; administration of immunoglobulins or any blood products; participation in a clinical study or use of an investigational compound; immunosuppressive or immunomodulatory medication, including systemic corticosteroids; and treatment with cytotoxic drugs.

Sample size was based on the criteria outlined in the FDA guidance, the margin of the non-inferiority for the GMT ratios was 1.5-fold and the margin of non-inferiority for the difference between the seroconversion rates was 10 percentage points. The study was designed to achieve 80% power over 6 co-primary endpoints. If a drop-out rate of 13% was assumed, recruiting 675 subjects per vaccine arm would result in 80% power over the 6 co-primary endpoints.

1474 participants were enrolled into the study and stratified by age into three cohorts:

- Cohort A (aged 6 months to less than 3 years), 710 participants;
- Cohort B (aged 3 to less than 9 years), 880 participants;
- Cohort C (aged 9 to less than 18 years), 402 participants

- Treatments

The 2009/2010 Northern Hemisphere formulation of CSL's IVV was supplied as a thimerosal-free aqueous suspension in pre-filled syringes. The two doses of CSL's IVV differed in injection volume and antigen content. Each 0.25 mL dose contained 7.5 mcg HA antigen for each of the three strains recommended by the World Health Organization for the 2009/2010 Northern Hemisphere influenza season. Each 0.5 mL dose contained 15 mcg HA antigen for each of the three recommended strains. Two half doses (0.25mL) doses were given to previously unvaccinated children 6 months to <3 years of age. Two full doses (0.5 mL) were given to previously vaccinated children 3-9 years of age. Previously influenza vaccinated children only received a single full or half dose respectively. Children 9-18 years of age were given a single full dose.

The comparator vaccine was Fluzone. This was given using the same dosage and vaccination schedule as described above.

- Outcomes/endpoints

**Primary endpoint:** The non-inferiority of CSL's IVV compared with Fluzone was assessed by the co-primary endpoints of geometric mean titer (GMT) and seroconversion rate for each strain contained within the vaccines as follows:

- The GMT ratio for the H1N1, H2N3 and B strains respectively.

- The difference between the seroconversion rates for the H1N1, H3N2 and B strains respectively.
- 

**Secondary Endpoints:** The safety and tolerability were assessed by determining the frequency, intensity and duration of:

- Solicited AEs for 6 days (total 7 days) following any study vaccination in each cohort;
- Unsolicited AEs for 29 days (total 30 days) following any study vaccination in each cohort;
- SAEs for 180 days following any study vaccination in each cohort;
- NOCIs for 180 days following any study vaccination in each cohort.

- **Statistical Methods**

CSL's IVV was considered to be non-inferior to Fluzone<sup>®</sup> if, for each strain:

- The upper bound of the two-sided 95% confidence interval (CI) on the ratio of the GMTs did not exceed 1.5-fold
- The upper bound of the two-sided 95% CI on the difference between the seroconversion rates did not exceed 10 percentage points.

➤ **Results**

- **Recruitment/ Number analysed**

**Planned:** 1350 participants (Cohort A: 450; Cohort B: 450; Cohort C: 450)

**Actual:** 1474 participants

**Table 1 Analysis Population, All Enrolled Participants**

Analysis Population	CSL's IVV			Fluzone <sup>®</sup>			Total N = 1474
	Cohort A n = 231	Cohort B n = 254	Cohort C n = 254	Cohort A n = 228	Cohort B n = 257	Cohort C n = 250	
Safety Population							
After the 1 <sup>st</sup> vaccination	229	252	254	228	255	250	1468
After the 2 <sup>nd</sup> vaccination	96	68	n.a.	110	78	n.a.	352
Evaluable Population	197	234	231	202	237	234	1335
Per-Protocol Population	195	229	230	201	236	233	1324

Abbreviation: n.a.; not applicable

- **Immunogenicity results**

Baseline GMTs for each of the three influenza strains contained in the study vaccines were similar between the vaccine groups and among the PP and Evaluable Populations. (Table 3).

For each analysis population, the GMT ratios for each influenza strain included in the study vaccines approximated 1, indicating that the immune response elicited by CSL's IVV was similar to that elicited by Fluzone. Furthermore, the upper bounds of the two-sided 95% CIs of the GMT ratios did not exceed 1.5-fold for all strains in each analysis population. Therefore, the non-inferiority criterion for GMT ratio was met for all three strains included in CSL's IVV. These results demonstrated that CSL's IVV was not inferior to Fluzone for the co-primary endpoint of GMT ratio.

The seroconversion rates for each of the three influenza strains included in the study vaccine were similar between the study vaccine groups and among each analysis population.

For each analysis population, the non-inferiority criterion for the difference in seroconversion rates between CSL's IVV and Fluzone<sup>®</sup> was met for all three strains. The upper bound of the two-sided 95% CI

on the difference between seroconversion rates did not exceed 10 percentage points. Furthermore, zero was included in the 95% CI, suggesting that there was no significant difference between the seroconversion rates elicited by CSL's IVV and Fluzone®. Therefore, CSL's IVV was not inferior to Fluzone® for the co-primary endpoint of difference in seroconversion rates.

**Table 3 Immune Responses after Vaccination with CSL's IVV or Fluzone®**

Influenza Strain / Variable	Per-Protocol Population	
	CSL's IVV n = 654 value (95% CI)	Fluzone® n = 670 value (95% CI)
<b>H1N1 (A/Brisbane/59/2007)</b>		
Baseline GMT	39.80 (35.39-44.76)	44.73 (39.78-50.29)
Post-vaccination GMT	385.49 (350.92-423.45)	382.45 (347.69-420.69)
GMFI	9.68 (8.61-10.89)	8.55 (7.62-9.59)
Ratio of GMFI for Fluzone® / CSL's IVV	0.88 (0.75-1.04)	
Seroconversion rate, % (95% CI)	70.2 (66.5-73.7)	66.0 (62.2-69.6)
Difference (Fluzone® - CSL's IVV), % (95% CI)	-4.2 (-9.2-0.8)	
<b>H3N2 (A/Uruguay/716/2007)</b>		
Baseline GMT	60.16 (51.86-69.78)	60.48 (52.49-69.69)
Post-vaccination GMT	669.13 (603.74-741.61)	705.61 (641.39-776.25)
GMFI	11.12 (9.90-12.50)	11.67 (10.41-13.07)
Ratio of GMFI for Fluzone® / CSL's IVV	1.05 (0.89-1.23)	
Seroconversion rate, % (95% CI)	74.9 (71.4-78.2)	76.9 (73.5-80.0)
Difference (Fluzone® - CSL's IVV), % (95% CI)	1.9 (-2.7-6.5)	
<b>B (B/Brisbane/60/2008)</b>		
Baseline GMT	12.46 (11.45-13.55)	12.40 (11.41-13.47)
Post-vaccination GMT	100.65 (90.45-112.00)	93.72 (84.30-104.19)
GMFI	8.08 (7.33-8.91)	7.56 (6.88-8.31)
Ratio of GMFI for Fluzone® / CSL's IVV	0.94 (0.82-1.07)	
Seroconversion rate, % (95% CI)	69.3 (65.6-72.8)	70.6 (67.0-74.0)
Difference (Fluzone® - CSL's IVV), % (95% CI)	1.3 (-3.6-6.3)	

Abbreviations: CI, confidence interval; CSL's IVV, CSL's Influenza Virus Vaccine; GMT, geometric mean titer; GMFI, geometric mean fold increase.

- **Safety results**

There were no deaths, and no vaccine-related SAEs or NOCIs reported during this study (Table 4). Enrollment halting rules were not triggered and there were no withdrawals due to safety events considered related to the study vaccine. There were no pregnancy or lactation reports received during the study. There was one withdrawal in this study due to an AE assessed as unrelated to study vaccine. The study also included 13 unrelated SAEs reported by 12 participants and 7 unrelated NOCIs reported by 7 participants (Table 4).

**Table 4 Summary of Adverse Events Reported after the First or Second Vaccinations**

Number of participants	CSL's IVV n = 735 n (%)	Fluzone® n = 733 n (%)	Total N = 1468 n (%)
One or more AEs	639 (86.9)	590 (80.5)	1229 (83.7)
Withdrawal due to an AE	1 (0.1)	0	1 (0.1)
Solicited AEs			
Any solicited local AEs	470 (63.9)	434 (59.2)	904 (61.6)
Any solicited systemic AEs	470 (63.9)	380 (51.8)	850 (57.9)
Unsolicited AEs <sup>a</sup>	311 (42.3)	266 (36.3)	577 (39.3)
Unsolicited AEs considered related to study vaccine <sup>b</sup>	81 (11.0)	48 (6.5)	129 (8.8)
SAEs	8 (1.1)	4 (0.5)	12 (0.8)
Deaths	0	0	0
SAEs considered related to study vaccine <sup>b</sup>	0	0	0
NOCIs	4 (0.5)	3 (0.4)	7 (0.5)
NOCIs considered related to study vaccine <sup>b</sup>	0	0	0

Abbreviations: AEs, adverse events; CSL's IVV, CSL's influenza virus vaccine; SAEs, serious adverse events; NOCIs, new onsets of chronic illness.

<sup>a</sup> Unsolicited AEs included unsolicited AEs from Day 0 to Day 29, and SAEs / NOCIs from Day 0 to Day 180 after the last dose of study vaccine.

<sup>b</sup> Related AEs were those assessed by the Investigator as having a causality of unknown, possibly, probably or definitely related to study vaccine.

### ***Solicited Local Adverse Events***

After the first vaccination, solicited local AEs were reported by 50.7%, 65.1%, and 68.5% of participants in Cohorts A, B and C, respectively. Overall, fewer participants in Cohorts A and B reported solicited local AEs after the second vaccination than after the first vaccination (Cohort A: 31.3% of participants; Cohort B: 35.3% of participants). In all cohorts and vaccine groups, pain, redness and induration / swelling were reported in decreasing order of frequency. The majority of participants reported solicited local AEs that were of mild intensity and short-lived. The proportion of participants reporting any of the solicited local AEs after administration with CSL's IVV was not significantly different to Fluzone®.

### ***Solicited Systemic Adverse Events***

After the first vaccination, solicited systemic AEs were reported by 74.7%, 55.6% and 56.7% of participants in Cohorts A, B and C, respectively (Table 12.9, 12.12 and 12.15). Fewer participants in Cohorts A and B reported solicited systemic AEs after the second vaccination than after the first vaccination. In Cohort A, the most frequently reported solicited systemic AE was irritability, while in Cohorts B and C the most frequently reported solicited systemic AE was myalgia. The majority of participants reported solicited systemic AEs that were of mild or moderate intensity and short-lived.

CSL's IVV elicited a higher frequency of some solicited systemic AEs than Fluzone®, particularly fever, irritability, loss of appetite and malaise. These differences were apparent in Cohorts A and B, but not in Cohort C. These differential effects were observed only after the first vaccination, and most AEs resolved within a short time frame. Of these solicited systemic AEs, fever (i.e., axillary temperature 99.5°F or more or oral equivalent) was associated with the greatest relative increase in risk in both Cohorts A and B. In Cohort A, participants who received CSL's IVV were 2.73 times as likely to develop fever than those who received Fluzone® (incidence of fever: CSL's IVV: 37.1% of participants; Fluzone: 13.6% of participants). In Cohort B participants who received CSL's IVV were 2.32 times as likely to develop fever than those

who received Fluzone® (incidence of fever: CSL's IVV: 21.8% of participants; Fluzone: 9.4% of participants).

**Table 12.9 Maximum Intensity of Solicited Systemic Adverse Events Reported after the First Vaccination by Participants in Cohort A (Safety Population)**

Solicited Systemic Adverse Event	CSL's IVV (N = 229)				Fluzone® (N = 228)			
	Mild	Moderate	Severe	All Grades	Mild	Moderate	Severe	All Grades
Any systemic AE, %	37.1	27.9	9.6	74.7	32.5	18.0	2.6	53.1
Fever, %	21.0	13.5	2.6	37.1	10.1	3.5	0.0	13.6
Nausea / Vomiting, %	3.1	6.1	2.6	11.8	4.8	2.2	0.4	7.5
Diarrhea, %	19.7	5.2	1.7	26.6	17.5	4.8	1.3	23.7
Loss of Appetite, %	20.5	10.0	1.3	31.9	16.2	3.1	0.4	19.7
Irritability, %	34.5	19.7	4.4	58.5	21.9	13.2	2.2	37.3

**Table 12.12 Maximum Intensity of Solicited Systemic Adverse Events Reported after the First Vaccination by Participants in Cohort B (Safety Population)**

Solicited Systemic Adverse Event	CSL's IVV (N = 252)				Fluzone® (N = 255)			
	Mild	Moderate	Severe	All Grades	Mild	Moderate	Severe	All Grades
Any systemic AE, %	32.9	17.5	5.2	55.6	32.9	10.2	1.2	44.3
Fever, %	13.1	7.5	1.2	21.8	8.2	0.8	0.4	9.4
Nausea / Vomiting, %	7.9	4.4	0.8	13.1	3.1	4.3	0.4	7.8
Diarrhea, %	6.0	0.8	0.0	6.7	7.8	1.6	0.0	9.4
Malaise, %	15.9	9.1	3.6	28.6	9.8	3.1	0.4	13.3
Headache, %	13.1	6.3	2.0	21.4	14.5	1.6	0.0	16.1
Myalgia, %	25.0	7.1	0.4	32.5	21.2	3.1	0.4	24.7

**Table 12.15 Maximum Intensity of Solicited Systemic Adverse Events Reported after a Single Vaccination by Participants in Cohort C (Safety Population)**

Solicited Systemic Adverse Event	CSL's IVV (N = 254)				Fluzone® (N = 250)			
	Mild	Moderate	Severe	All Grades	Mild	Moderate	Severe	All Grades
Any systemic AE, %	35.8	14.6	6.3	56.7	31.6	16.4	2.4	50.4
Fever, %	3.1	2.4	0.8	6.3	2.8	1.2	0.0	4.0
Nausea / Vomiting, %	7.5	0.4	1.2	9.1	6.4	2.0	1.2	9.6
Diarrhea, %	5.9	1.6	0.4	7.9	8.8	1.2	0.0	10.0
Malaise, %	11.4	6.3	3.9	21.7	12.0	7.2	1.2	20.4
Headache, %	17.3	7.1	2.8	27.2	18.4	6.8	1.2	26.4
Myalgia, %	30.7	7.1	2.0	39.8	26.8	8.8	1.6	37.2

### **Unsolicited Adverse Events**

More participants in the CSL's IVV group than the Fluzone® group reported unsolicited AEs after vaccination (Table 4). The three most frequently reported unsolicited AEs reported in participants receiving either study vaccine were cough, pyrexia and rhinorrhea (Cohorts A and B), and cough, oropharyngeal pain and headache (Cohort C).

**MAH's Conclusions:**

This study demonstrated that the immune response to CSL's IVV was robust and was not inferior to that of another influenza vaccine (Fluzone®) licensed for use in children aged 6 months to less than 18 years. Therefore, it can be expected that CSL's IVV offers a level of clinical protection against influenza infection in children that is not inferior to currently licensed influenza vaccines in the US.

There were no deaths, and no vaccine-related SAEs or NOCIs reported during this study. Overall, no significant differences in local reactogenicity were observed between CSL's IVV and Fluzone®. The majority of participants reported solicited local AEs that were of mild intensity and short-lived. In all cohorts and both vaccine groups, the most frequently reported solicited local AE was pain.

CSL's IVV elicited a higher frequency of some solicited systemic AEs than Fluzone, particularly fever, irritability, loss of appetite and malaise. The differences between the study vaccines were apparent in Cohorts A and B, but not in Cohort C. These differential effects were observed only after the first vaccination, and most AEs resolved within a short time frame. Of these solicited systemic AEs, fever was associated with the greatest relative increase in risk in both Cohorts A and B.

More participants in the CSL's IVV group than in the Fluzone® group reported unsolicited AEs after vaccination. The most commonly reported unsolicited AE in all cohorts and vaccine groups was cough, followed by pyrexia and rhinorrhea (Cohorts A and B), and oropharyngeal pain and headache (Cohort C).

*Assessor's comment: In general the rapporteur agrees with the conclusions regarding immunogenicity. However, the increased risk of fever reactions in children less than 9 years of age who received CSL's IVV compared to the comparator group is of great concern. In addition to fever, other systemic reactions were also increased in cohorts A and B.*

**CSLCT-CHF-06-25** An Observer-Blind, Randomized, Comparator-Controlled, Single-Centre Study to Evaluate the Tolerability, Safety, and Immunogenicity of Inactivated Influenza Vaccine, CSL Limited in a Healthy Pediatrics and Adult Population (aged  $\geq 3$  years to  $\leq 80$  years)

**➤ Description**

This study was conducted in 2007 at a single site in China. The study included 690 participants aged from 3 years to 80 years.

**➤ Methods**

- Objective(s)
  - Observe the tolerance of CSL investigational vaccine.
  - To evaluate the safety of CSL Inactivated Influenza Vaccine in a healthy Paediatric and Adult population including elderly ( $\geq 3$  years age  $\leq 80$  years)
  - To evaluate the immunogenicity of CSL Inactivated Influenza Vaccine in healthy Children and adults ( $\geq 3$  years age  $\leq 80$  years).
- Study design
  - Phase I trial: Only investigational vaccine was applied for tolerance observation. 30 eligible volunteers were selected. The trial was open design without the control arm. The adverse reactions

- Phase III trial : It was an observer blind, randomization and parallel control trial to compare both safety and immunogenicity between CSL influenza vaccine and control vaccine from GSK manufactured. The subjects needed to have blood drawn at day 0 before injection and day 21 post injection for immunogenicity assessment of HI antibody.

All subjects were assessed in according with following age groups since the different criteria of immunogenicity:

Child: age  $\geq 3$  years and  $< 16$  years  
 Adult: age  $\geq 16$  years and  $< 60$  years  
 Elderly: age  $\geq 60$  years and  $\leq 80$  years

- Study population /Sample size**  
 Healthy subjects between 3 and 80 years of age.

Hypersensitivity to eggs, chicken protein, neomycin, polymyxin or any components of the vaccine;

Influenza vaccination in the previous 6 months;

Clinical signs of active infection and/or an axillary temperature of  $>37.1^{\circ}\text{C}$  at study entry,

The Phase I trial aimed to recruit 30 subjects and only for Fluvax. Considering 2:1 ration for the test and comparator groups, drop-out rate during the trial and randomization block length (6-fold), the study recruited 690 participants in order to meet SFDA requirement of at least 500 subjects, of them 460 for Fluxax group and 230 for the comparator group.

The trial included three age groups as follows:

	Phase (3~80y)	Phase		
		Child (3~16y)	Adult (18~60y)	elderly (>60y)
Fluvax	30	184	184	92
comparator	0	92	92	46
<b>Total</b>	<b>30</b>	<b>690</b>		

- Treatments**  
 Test: Fluvax CSL  
 Control: Flurix  
 A single dose of 0.5 nL was given to all subjects.

- Outcomes/endpoints**

All participants were on site for observation 30 min for immediate reactions, then the subjects were asked to record their local and systemic reaction at 6h, 24h, 48 and 72 h post vaccination. All adverse events were followed up to day 28.

#### Safety endpoints

Safety observation included solicited and unsolicited systemic and local adverse events post vaccination. Main solicited systemic and local reactions were fever and Erythema. Other solicited systemic reaction included headache, fatigue, myalgia/arthralgia, cough, allergic reaction, nausea, vomiting, abdominal pain and diarrhea, local solicited reactions were rash, ecchymosis and pain at injective area.

#### Immunogenicity endpoints

Following measurement of serum HI antibody at day 21 post vaccination.:

Seroconversion and Seroprotective percentage were major evaluation endpoints ; but the HI antibody GMT increase also would be observed;

\* definition of seroconversion :

A post-vaccination titer of >1: 40 for those with a pre-vaccination HI titre of <1:10 (seroconversion) and as a fourfold or greater increase in HI titre for those with a pre-vaccination HI titre of >1:10.

\* definition of seroprotection :

Antibody titre (HI) of subject should be >1:40 post vaccination.

- **Statistical Methods**

Safety:

Described statistics presented all safety results of safety set population including all incidence and frequency of adverse events within 72 hours post vaccination , follow up any any adverse events from day 4 to day 28 post vaccination.

Statistical comparison of all adverse events incidence and frequency at both vaccine groups.

Immunogenicity

The following statistics are used in the evaluable population from serological measurement for each of antigen strain :

1) Geometric mean of pre-vaccination serum HI titers and 95% Confidence Intervals .

2) Number and percentage of evaluable participants with pre-vaccination serum HI titers  $\geq 1 : 40$  (seroprotection rate).

3) Geometric mean and 95% Confidence Intervals of post-vaccination serum HI titers.

4) Seroconversion or significant increases percentage of evaluable participants and 95% Confidence Intervals in HI antibody titer.

5) Geometric Mean increase.

6) seroprotection rate post-vaccination and 95% Confidence Intervals.

➤ **Results**

- **Recruitment/ Number analysed**

690 subjects enrolled randomly in the trial III, including 460 subjects for CSL vaccine and 230 for comparator. All 690 subjects completed one vaccine injection and provided their safety data. All of them deposited into safety analysis set.

As 80 individuals of them did not provided their blood sample at day 21 post vaccination, those subjects were withdrawn from FAS analysis set, overall drop-out rates was 12.39%(57/460) of the test group and 10.0% (23/230)of the comparator arm. Finally, 610 participants entered into FAS (CSL vaccines 403 , the comparator 207), no significant statistical difference between vaccine groups.

One kid subject (CRF 163) was excluded from PP population due to the participant having a higher H3N2 titer (1:1520) at baseline than post vaccination(1:1280). 609 subjects enrolled PP analysis Set at end (CSL vaccine group 402, The comparator 207).

- **Immunogenicity results**

The baseline titres were comparable between groups. The seroconversion rates, seroprotection rates, and geometric mean increase of HI antibody titres for the paediatric population are shown in Tables 7.2, 7.3 and 7.4.

**Table 7.2 Comparison of seroconversion post vaccination**

Groups	N	H1N1				H3N2				B			
		SC (n)	SC (%)	Com. of groups		SC (n)	SC (%)	Com. of groups		SC (n)	SC (%)	Com. of group	
				Statistics	P			Statistics	P			Statistics	P
Child	T	171	149	87.13	0.6891	110	64.33	1.0000	134	78.36	0.0661		
	C	83	74	89.16		54	65.06		56	67.47			

**Table 7.3 Comparison of seroprotection post vaccination**

Groups	N	H1N1				H3N2				B			
		≥1:40 N	%	Comparison among groups		≥1:40 N	%	Comparison among groups		≥1:40 N	%	Comparison among groups	
				statistics	P			statistics	P			statistics	P
Child	T	171	168	98.25	0.0157	168	98.25	0.6629	153	89.47	0.5329		
	C	83	76	91.57		81	97.59		72	86.75			

**Table 7.4 Geometrics Mean Titer increase (fold) of HI antibody post vaccination**

Groups	N	H1N1				H3N2				B			
		Ab GMT (1: X)		Ab increase (fold)	An GMT (1: X)		Ab increase (fold)	Ab GMT (1: X)		Ab increase (fold)			
		pre	post		pre	post		pre	post				
Child	T	171	50.2	680.1	13.6	74.7	440.8	5.9	13.7	151.2	11.1		
	C	83	39.0	908.9	23.3	78.7	519.4	6.6	14.0	100.2	7.2		

- Safety results

The results for fever reactions are presented below:

**Table 6.1 Fever incidence in the age groups**

	Group	N	Mild		Moderate		Overall		Comparison between groups Total reaction rate	(Fisher test) reaction ≥ moderate
			N	%	N	%	N	%		
Child	T	184	3	1.63	2	1.09	5	2.72	1.0000	0.5549
	C	92	3	3.26	0	0.00	3	3.26		
Adult	T	184	7	3.80	1	0.54	8	4.35	1.0000	1.0000
	C	92	4	4.35	0	0.00	4	4.35		
Elderly	T	92	6	6.52	0	0.00	6	6.52	0.5059	0.3333
	C	46	4	8.70	1	2.17	5	10.87		
Overall	T	460	16	3.48	3	0.65	19	4.13	0.5600	1.0000
	C	230	11	4.78	1	0.43	12	5.22		

**Table 6.3 Local reaction summary**

Symptoms	Group	N	Mild		Moderate		Severe		Total		Comparison of groups (Fisher exact) Total incidence ≥ II°	
			n	%	n	%	n	%	n	%		
Erythema	T	460	1	0.43	1	0.22	0	0.00	2	0.43	1.0000	1.0000
	C	230	1	0.43	0	0.00	0	0.00	1	0.43		
Pain	T	460	9	1.96	0	0.00	0	0.00	9	1.96	0.3523	--
	C	230	2	0.87	0	0.00	0	0.00	2	0.87		
Induration	T	460	2	0.43	0	0.00	0	0.00	2	0.43	1.0000	--
	C	230	1	0.43	0	0.00	0	0.00	1	0.43		
Swelling	T	460	4	0.87	1	0.22	1	0.22	6	1.30	1.0000	0.5549
	C	230	3	1.30	0	0.00	0	0.00	3	1.30		
Ecchymosis	T	460	0	0.00	0	0.00	0	0.00	0	0.00	0.3333	--
	C	230	1	0.43	0	0.00	0	0.00	1	0.43		

MAH overall conclusion: The trial demonstrated that Australian CSL influenza vaccine Fluvax was none of vaccination relative serious adverse events, safety evaluation showed there was no statistical difference compared to the comparator vaccine from GSK manufactured. The assessment of serological conversion rate, seroprotection and Geometric Mean Titer increase of HI antibodies reached expecting efficacy of the protocol and EMEA criteria. CSL vaccine was suitable for population aged from 3 to 80 on prevention of seasonal influenza.

*Assessor's comment: The results of this Chinese study differs from the other studies. The overall reactogenicity and adverse events reporting was considerably lower than in other studies and no specific concern was raised from the presented results.*

### 3. Discussion on clinical aspects

- The immunogenicity results are generally as can be expected, and where a comparator is available, the differences are very small. However, the rates of fever and other systemic reactions in paediatric subjects causes concern. There was a considerable difference compared to the control vaccine in study CSLCT-USF-07-36 both for children 6 months to 3 years and the 3-9 year old children. The systemic reaction rates were similar in both studies CSLCT-USF-06-29 and CSLCT-USF-07-36. No other major differences in reactogenicity between control and test vaccine, or other safety signals were detected.

In addition to the results of these studies, post-marketing surveillance during the 2010 Southern Hemisphere influenza season suggested a disproportionate number of reports of febrile seizures and febrile events for recipients of CSL's IVV compared to previous years. The reports were predominantly from children six months to less than five years of age. Although febrile events were also observed in children five to less than nine years of age, it was at a rate much lower than that reported in children less than five years of age. Findings from the 2010 post-marketing surveillance was not consistent with the pediatric safety and tolerability profile of CSL's IVV observed in the clinical safety database or to the post-marketing reports prior to 2010. Regulatory actions have been taken to minimize the risks of febrile seizures and febrile reactions associated with CSL's IVV in children less than five years of age. Thus, an age restriction not to use Afluria/ENZIRA in children up to 5 years has been applied to the current approval in the EU (MRP, SE RMS).

## **V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION**

### **➤ Overall conclusion**

The results of these studies raise concern regarding the incidence of fever and other systemic reactions in children less than 9 years of age following vaccination with Afluria/ENZIRA. A type II variation to include additional information in the SPC regarding increased reporting of fever in children from 5 to 9 years of age has recently been finalised. The root cause of this safety issue in young children has not been found yet and it is stressed that this is very important to identify, as it is unknown if also more severe reactions might occur in other age groups.

### **➤ Recommendation**

No further action required