RESULT SUMMARY

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)

Protocol No.: CSLCT-FLU-04-05

EudraCT No.: 2015-004820-69

Study Product: Inactivated Influenza Vaccine

Indication: Prevention of Influenza Caused by Influenza Virus Types A and B

Sponsor: CSL Limited
45 Poplar Road Parkville VICTORIA 3052

Principal Investigator: Professor Terry Nolan
Investigator: Dr Peter Richmond

Date of First Enrolment: 07 March 2005 (Primary Vaccination Series)
Date of First Booster Vaccination: 27 February 2006 (Booster Vaccination Series)
Date of Last Participant Completed: 12 June 2006 (Booster Vaccination Series)

PRIMARY VACCINATION SERIES - SUMMARY

Name of Company: CSL Limited

Name of Finished Product: Inactivated Influenza Vaccine

Name of Active Ingredient: 45 mcg of Influenza haemagglutinin antigens (15 mcg each of H1N1, H3N2 and B strains)

Title of Study: 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).

Investigators:

• Professor Terry Nolan

• Dr Peter Richmond

Study Centre(s):

• Murdoch Childrens Research Institute, Royal Children's Hospital, Flemington Road, Parkville, VIC 3052 Australia

• Princess Margaret Hospital for Children, Roberts Rd, Subiaco, WA 6008 Australia

Publication (reference): Not applicable

Study Period:

Date of first enrolment: 07 March 2005

Date of last completed: 01 July 2005

Phase of development: III

Objectives: The primary objective was to evaluate the safety of CSL's Inactivated Influenza Vaccine in a paediatric population (≥6 months to <3 years and ≥3 years to <9 years) through the assessment of the frequency of:

• Local and systemic solicited AEs for 7 days post each vaccination

• Unsolicited Adverse Events (unsolicited AE) for 30 days post each vaccination

• Serious Adverse Events (SAE) for 6 months after the last primary vaccination.

The secondary objective was to evaluate the immunogenicity of CSL's Inactivated Influenza Vaccine in a paediatric population (≥6 months to <3 years and ≥3 years to <9 years) according to the criteria of the CPMP/BWP/214/96 Note for Guidance on Harmonisation of Requirements for Influenza Vaccines.

Methodology:

Multi-Centre, Open Label Study. The study was to be conducted in accordance to CPMP/BWP/214/96 Note for Guidance on Harmonisation of Requirements for Influenza Vaccines for individuals aged ≥18 to <60 years of age.

Primary Vaccination Series:

Day 0 (Day of Vaccination, Dose 1):

Written informed consent was obtained from the child's parent(s) or guardian(s) prior to undertaking protocol-related assessments and procedures. A review of the participant's medical history, including details of any concomitant medications and vaccinations, previous influenza vaccination status and details of previous history of influenza-like illness, was obtained. A brief medical evaluation, including a physical examination if clinically indicated, was conducted. The participant's temperature was measured and recorded (axillary temperature for children aged less than 5 years and oral temperature for children aged 5 years and older), and a 5 mL blood sample was collected for the determination of baseline antihaemagglutinin antibody titre. Participant eligibility was assessed by reviewing inclusion/exclusion criteria. Eligible participants were assigned to either Group A (≥6 months to <3 years) or Group B (≥3 years to <9 years), allocated the next available unique participant number, and given a single dose of Inactivated Influenza Vaccine of either 0.25 mL (Group A) or 0.5 mL (Group B) delivered by intramuscular injection into the anterolateral aspect of the thigh for participants 12 months or younger and into the deltoid region of the arm for participants older than 12 months of age. Participants were observed for 30 minutes post-vaccination for rare anaphylactic reactions.

Day 0-7:

The participant's parent(s)/guardian(s) was issued with a Dose 1, 7-day post-vaccination Solicited Adverse Events (AE) Diary Card and a Dose 1, 30-day post-vaccination Unsolicited AE Diary Card (including a local reaction measurement card). A digital thermometer was also issued and parent(s)/guardian(s) were instructed on how to measure and record the participant's temperature and how to recognise signs/symptoms of flu-like illness. The participant's parent(s)/guardian(s) completed the Dose 1, 7-day Diary Card once a day for 7 days, commencing on Day 0 (Dose 1, vaccination day), and returned the Solicited AE Diary Card to the Principal Investigator (PI)/delegate at the end of the 7-day period in a pre-stamped, pre-addressed envelope. An appointment was made for each participant to return for their second vaccination on Day 30 ± 3.

Day 10 ± 2:

Parent(s)/guardian(s) of participants who had not returned their Dose 1, 7-day post-vaccination Solicited AE Diary Card by Day 10 ± 2 were contacted by the PI/delegate and every effort was made to collect the Diary Cards. Solicited and unsolicited AEs and SAEs were assessed.

Day 30 ± 3:

The participant's parent(s)/guardian(s) completed the Dose 1, 30-day post-vaccination Unsolicited AE Diary Cards and returned with their child on Day 30 ± 3 for their second vaccination. Prior to receiving the second vaccination dose, the occurrence of SAEs was assessed. The participant's ongoing eligibility was reviewed, including a brief medical evaluation (with physical examination if

clinically indicated). The participant's temperature was measured and recorded (axillary temperature for children aged less than 5 years and oral temperature for children aged 5 years and older), and a 5 mL blood sample collected for the determination of post-vaccination antibody titres.

The participant received a second vaccination dose of Inactivated Influenza Vaccine of either 0.25 mL (Group A) or 0.5 mL (Group B). The participant was observed for 30 minutes post-vaccination for rare anaphylactic reactions. The participant's parent(s)/guardian(s) was issued with a Dose 2, 7-day postvaccination Solicited AE Diary Card and a Dose 2, 30-day post-vaccination Unsolicited AE Diary Card.

Day 60 ± 3 (Primary Vaccination Exit Evaluation):

The participant's parent(s)/guardian(s) completed and returned the Dose 2, 7-day post-vaccination Solicited AE Diary Card and Dose 2, 30-day post-vaccination Unsolicited AE Diary Card. A 5 mL blood sample was collected for the determination of post-vaccination antibody titres. The PI/delegate assessed occurrence of SAEs and all related AEs were followed up until resolution or stabilisation. All participants underwent a brief medical evaluation, including a physical examination where clinically indicated, prior to study exit.

Booster Vaccination:

Day 365 ± 14:

A single booster vaccination will be administered 12 months after the primary vaccination (March 2006) and the results described in the Final (Addendum) Analysis.

Intercurrent Flu-like Illness Visit

The criteria for a flu-like illness were as follows:

• Axillary temperature ≥ 37.5°C or oral temperature ≥ 38. 0°C, and

• At least one of the following flu-like symptoms: headache, cough, sore throat, rhinitis, wheezing/shortness of breath, myalgia, earache, vomiting/diarrhoea, reduced appetite and irritability.

Parent(s)/guardian(s) of participants experiencing signs/symptoms of an intercurrent flu-like illness at any time between the first dose of Study Vaccine and the Primary Exit Evaluation were instructed to attend an additional visit for medical confirmation of the flu-like illness. Following confirmation of symptoms, attempts were made to isolate virus present in the respiratory tract by obtaining throat swab specimens within four days of onset of symptoms.

Number of Subjects (planned and analysed):

Planned: 300 participants [150 Group A (≥6 months to <3 years) and 150 Group B (≥3 years to <9 years)], in accordance with the number specified by the Swedish Medical Products Agency (MPA).

Analysed: 298 participants (151 Group A and 147 Group B) were analysed for safety; 287 participants (143 Group A and 144 Group B) were analysed for immunogenicity following the initial dose at Day 0; 271 participants (139 Group A and 132 Group B) were analysed for immunogenicity following a second dose at Day 30 ± 3. A total of 293 participants completed the study.

Diagnosis and main criteria for inclusion:

• Healthy male or female children, aged ≥6 months to <9 years at the time of first study vaccination

• Provision of written informed consent by parent(s)/guardian(s) to participate in the study

• Ability 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).

Test product, dose and mode of administration, batch number:

Test product is Inactivated Influenza Vaccine.

Dose:

Primary Vaccination Series (Days 0 and 30 ± 3):

Group A: 2 x 0.25 mL vaccinations 30 days apart

Group B: 2 x 0.5 mL vaccinations 30 days apart

Booster Vaccination (Day 365 ± 14):

<3 years of age at time of booster vaccination: 1 x 0.25 mL

≥3 years of age at time of booster vaccination: 1 x 0.5 mL

Mode of Administration:

Children aged 12 months of age or younger: intramuscular injection into the anterolateral aspect of the thigh. Children older than 12 months of age: intramuscular injection into the deltoid region of the arm.

Duration of treatment: In the Primary Vaccination Series, a single dose was administered on Day 0 and Day 30 ± 3 (2 doses).

Reference therapy, dose and mode of administration, batch number: Not applicable.

Criteria for Evaluation:

The safety analysis included all participants who received at least one dose of the Study Vaccine consistent with the prescribed dose for their age group. The immunogenicity analysis included all participants who received at least one dose of the Study Vaccine, had evaluable pre- and at least one post-vaccination result, had no lab-confirmed influenza like illness episodes and had received the Study Vaccine consistent with the prescribed dose for their age group.

Immunogenicity:

Haemagglutinin inhibition (HI) and Single Radial Haemolysis (SRH) assays were performed on pre and post-vaccination serum samples obtained from the participants, and the data collected were used to determine immunogenicity according to the criteria set down in the CPMP/BWP/214/96 Note for

Guidance on Harmonisation of Requirements for Influenza Vaccines for individuals aged ≥18 to <60 years of age. These criteria were used to assess immunogenicity in a paediatric population ≥6 months to <9 years of age. The immunogenicity of CSL's Inactivated Influenza Vaccine for each age cohort (Group A (≥6 months to <3 years) and Group B (≥3 years to <9 years)) was demonstrated for each of the three strains with at least one of the following criteria being met:

• More than 40% of participants in each age cohort sero-convert or demonstrate a significant increase in antihaemagglutinin antibody titre (HI or SRH assay)

• A mean geometric increase in antihaemagglutinin antibody titre (HI) or SRH arithmetic mean zone annulus area (AMZAA) of greater than 2.5 fold

• More than 70% of participants in each age cohort has a post-vaccination antihaemagglutinin antibody titre (HI) greater than or equal to 40 or SRH AMZAA greater than 25 mm^2. The HI assay was conducted on all three influenza strains contained within the vaccine (H1N1, H3N2 and B), whereas the SRH assay was conducted on the B strain only.

Safety:

Safety was assessed based on the occurrence of solicited local and systemic AEs and unsolicited AEs. Medical evaluation, oral temperature, solicited local and systemic AEs, unsolicited AEs (recorded on the Dairy Card or reported during study visits) and SAEs were recorded. The AE data were collated and analysed.

Statistical Methods: No inferential statistics were used. Statistical analyses for both immunogenicity and safety results comprised summary and descriptive statistics. Summaries were tabulated for demographic and clinical data.

Summary – Conclusions

Immunogenicity Results:

For the HI assay, the Study Vaccine met at least one of the CPMP criteria for all three influenza strains in both age groups (≥6 months to <3 years of age and ≥3 to <9 years of age). This result was achieved following Dose 1 and Dose 2. The responses to the HI assay following Dose 2 were consistently higher than those observed following Dose 1 such that each of the three CPMP criteria were met across each of the three strains.

For the SRH assay, the Study Vaccine met at least one of the CPMP criteria for the B strain in both age groups. The responses to the SRH assay following Dose 2 were consistently higher than those observed following Dose 1.

Safety Results:

Overall, CSL's Inactivated Influenza Vaccine was safe and well tolerated in a paediatric population (≥6 months to <9 years of age). The first occurrence of all solicited local AEs were considered related to the Study Vaccine, and all subsequent occurrences were to be assessed by the PI/delegate with respect to causality. Overall, all solicited local AE were related to the study vaccine. In Group A (≥6

months to <3 years of age) and Group B (≥3 years to <9 years of age) following Dose 1 and 2, Pain and Redness were the most commonly reported solicited local AEs, whereas Rhinitis and Irritability were the most frequently reported solicited systemic AEs. The majority of systemic AEs were considered possibly, probably or definitely related to the Study Vaccine.

A total of 658 unsolicited AEs were reported in the Safety population (n= 298); 388 in Group A and 270 in Group B. Seventy-six events (11.6%) were assessed by the PI/delegate as possibly, probably or definitely related to the Study Vaccine. Of the total number of unsolicited AEs reported 309 (47%) were assessed as mild, 273 (41.5%) as moderate and 76 (11.6%) as severe. No participants withdrew as a result of an adverse event. Three SAEs occurred within the 30 day post-vaccination period postdose 1 or post-dose 2. All SAEs were assessed by the PI/delegate as not related to the Study Vaccine.

Conclusion :

The primary objective of the study was to determine the safety of CSL's Inactivated Influenza Vaccine in a paediatric population (≥6 months to <9 years of age). The majority of the vaccine-related adverse events were of a mild intensity. The PI/delegate assessed the three SAEs reported as not related to the Study Vaccine. No deaths occurred during the study period.

The secondary objective of the study was to evaluate the immunogenicity of CSL's Inactivated Influenza Vaccine in paediatric participants (≥6 months to <9 years of age) according to the CPMP/BWP/214/96 Note for Guidance on Harmonisation of Requirements for Influenza Vaccines. For the HI assay, the vaccine met the CPMP criteria for all three influenza strains in both age groups (≥6 months to <3 years of age and ≥3 to <9 years of age). This result was achieved following Dose 1 and Dose 2. The responses to the HI assay following Dose 2 were consistently higher than those observed following Dose 1 such that each of the three CPMP criteria was met across each of the three strains. For the SRH assay, the vaccine met the CPMP criteria for the B strain in both age groups. The responses to the SRH assay following Dose 2 were consistently higher than those observed following Dose 1. In conclusion, CSL's Inactivated Influenza Vaccine is generally safe, well tolerated and immunogenic in children aged ≥6 months to <9 years.

Date of the Report: 26 September 2005

BOOSTER VACCINATION SERIES - SUMMARY

Name of Company: CSL Limited

Name of Finished Product: Inactivated Influenza Vaccine

Name of Active Ingredient: 45 μg of Influenza Haemagglutinin Antigens (15 μg each of H1N1, H3N2 and B strains)

Title of Study: 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).

Principal Investigator: Professor Terry Nolan

Investigator: Dr Peter Richmond

Study Centre(s): 2 sites

Site 01: Murdoch Childrens Research Institute, Royal Children's Hospital, Flemington Road, Parkville, VIC 3052 Australia

Site 02: Princess Margaret Hospital for Children, Roberts Rd, Subiaco, WA 6008 Australia

Publication (Reference): Not applicable

Study Period:

This study consisted of two phases - a Primary Vaccination Series (consisting of a two-dose vaccination regimen) and a booster vaccination 12 months following the date of the first vaccine dose. The outcomes of the Primary Vaccination Series were documented in a comprehensive Clinical Study Report (CSR) dated 26 September 2005. This CSR documents evaluation of the immunogenicity and safety outcomes of the Booster Vaccination Series.

Booster Vaccination Series: Days 365 (± 14) to 395 (± 3) days after the initial primary vaccination, on study period 30 ± 3 days.

Date of First Enrolment- Primary Vaccination Series: 07 March 2005

Date of First Booster Vaccination: 27 February 2006

Date of Last Participant Completed: 12 June 2006

Phase of Development: III

PRIMARY OBJECTIVE:

To evaluate the safety of CSL's Inactivated Influenza Vaccine in a paediatric population through assessment of the frequency of:

• Local and systemic solicited adverse events (AEs) for 7 days post-booster vaccination;

• Unsolicited adverse events (unsolicited AEs) for 30 days post-booster vaccination, and

• Serious adverse events (SAEs) for 6 months post-booster vaccination.

SECONDARY OBJECTIVE:

To evaluate the immunogenic response to CSL's Inactivated Influenza Vaccine in a paediatric population according to the criteria specified in the CPMP/BWP/214/96 Note for Guidance on Harmonisation of Requirements for Influenza Vaccines.

METHODOLOGY:

This was a multi-centre, open label study conducted over two distinct phases; a Primary Vaccination Series (a two dose vaccine regimen) and a Booster Vaccination Series (a single booster vaccine dose).

Booster Vaccination Series:

Approximately 12 months after receiving the first vaccination dose, participants returned to the Study Sites for administration of a single dose of booster vaccine.

Booster Vaccination (Day 365 ± 14 after initial primary vaccination):

The participant's ongoing eligibility was assessed prior to administration of the Booster Dose. The Principal Investigator (PI)/delegate reviewed the participant's medical history, conducted a medical/physical examination where indicated, and recorded the participant's temperature (axillary temperature for children aged <5 years and oral temperature for children aged ≥5 years). The PI/delegate determined the occurrence of flu-like illness in each participant during the off-study period, and, in cases where a participant experienced symptoms, determined whether the flu-like illness was virologically confirmed. For eligible participants, a 5 mL blood sample was collected for the determination of pre-booster vaccination antibody titre. The participant received either 0.25 mL (Group A: participants aged ≥6 months to <3 years) or 0.5 mL (Group B: participants aged ≥3 years to <9 years) of a Booster Dose of Inactivated Influenza Vaccine. Where a participant turned 3 years of age in the interval between the Primary Vaccination Series exit evaluation (Visit 3; Day 60 ± 3) and the Booster Vaccination Series (Visit 4; Day 365 ± 14), the participant was included in the Group B treatment arm and the volume of the third vaccination dose was increased to 0.5 mL. Where possible, the Study Vaccine was administered into the arm contralateral to where the blood specimen was collected.

Post Vaccination

The participant was observed for 30 minutes post-booster vaccination to monitor for rare anaphylactic reactions. The participant's parent(s)/guardian(s) was issued with a Booster Dose, 7-day post-booster vaccination Solicited AE Diary Card and a Booster Dose, 30-day post-booster vaccination Unsolicited AE Diary Card (including a local reaction measurement card). The participant's parent(s)/guardian(s)

completed the Booster Dose, 7-day Diary Card once a day for 7 days, commencing on Day 0 (vaccination day), and returned the Solicited AE Diary Card to the PI/delegate at the end of the 7-day

period in a pre-stamped, pre-addressed envelope. An appointment was made for each participant to return for the 1 month post-booster vaccination blood draw.

Exit Evaluation (Day 30 ± 3 After Booster Vaccination)

The participant's parent(s)/guardian(s) completed the Booster Dose, 30-day post-booster vaccination Unsolicited AE Diary Cards and returned with their child approximately 1 month post-booster vaccination (Visit 5) to provide a 5 mL blood specimen for determination of post-booster vaccination antibody titres. The PI/delegate assessed SAE occurrences and followed up all related AEs until resolution or stabilisation. All participants underwent a brief medical evaluation prior to study exit. A physical examination was performed where clinically indicated.

Intercurrent Influenza-Like Illness Visit

The criteria for a flu-like illness were as follows:

• Axillary temperature ≥37.5°C or oral temperature ≥38. 0°C, and

• At least one of the following flu-like symptoms: headache, cough, sore throat, rhinitis, wheezing/shortness of breath, myalgia, earache, vomiting/diarrhoea, reduced appetite and irritability.

Parent(s)/guardian(s) of participants experiencing signs/symptoms of an intercurrent flu-like illness at any time between the booster vaccination and the exit evaluation were instructed to attend an additional visit for medical confirmation of the flu-like illness. Following confirmation of symptoms, attempts were made to isolate the virus present in the respiratory tract by obtaining throat swab specimens within four days of onset of symptoms.

NUMBER OF PARTICIPANTS:

Planned for Primary Vaccination Series: 300 participants [Group A (≥6 months to <3 years)= 150 and Group B (≥3 years to <9 years)= 150], in accordance with the number specified by the Swedish Medical Products Agency (MPA).

Analysed in Primary Vaccination Series: 298 participants were analysed for safety (Group A = 151 and Group B = 147); 287 participants were analysed for immunogenicity following the initial dose at Day 0 (Group A = 143 and Group B = 144); 271 participants were analysed for immunogenicity following a second dose at Day 30 ± 3 (Group A = 139 and Group B = 132), and a total of 293 participants completed the study.

Analysed in Booster Vaccination Series: 273 participants received the Booster Dose [Group A (>6 months to <3 years) = 76 and Group B (≥3 years to <9 years) = 197]; 272 were analysed for safety (Group A = 76 and Group B = 196); 235 were analysed for immunogenicity (Group A = 61 and Group B = 174), and 266 completed the study (Group A = 74 and Group B = 192). Of the 273 participants who received the Booster Dose, 231 were from Site 01 (84.6%; Group A = 65 and Group B = 166), and 42 were from Site 02 (15.4%; Group A = 11 and Group B = 31).

CRITERIA FOR INCLUSION IN BOOSTER VACCINATION SERIES:

A participant was excluded from receiving the Booster Vaccination where he/she met any one of the following criteria:

• Had developed an allergy to eggs, chicken feathers, neomycin, polymyxin, or any components of the vaccine;

• Had experienced clinical signs of active infection and/or an axillary temperature of ≥37.5°C or oral temperature of ≥38°C at study entry. Booster Vaccination may have been deferred for such individuals, at the discretion of the PI;

• Had developed a suspected immunosuppressive condition (including cancer), or a previously diagnosed (congenital or acquired) immunodeficiency disorder (including HIV);

• Was receiving or had received (within the 90 days prior to receiving the Study Vaccine) treatment with immunosuppressive or immunomodulative medication, including systemic corticosteroids, as follows; chronic or long term corticosteroids: ≥0.5 mg/kg/day of oral prednisolone or equivalent (Note: Use of topical or inhalant corticosteroids prior to administration of the Study Vaccine or throughout the study was acceptable);

• Had received immunoglobulins and/or any blood products since exiting the primary phase of the study or had plans to receive such blood products during the study period;

• Had participated in a clinical study or use of an investigational compound (i.e. a new chemical or biological entity not registered for clinical use) within the 90 days prior to receiving the Study Vaccine or was planning to enter such a study during the study period;

• Was receiving treatment with cytotoxic drugs or treatment within the 6 months prior to administration of the Study Vaccine;

• Had a known history of Guillain-Barré Syndrome;

• Had a major congenital defect or serious illness, and

• Had a history of neurologic disorders or seizures.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Test Product: Inactivated Influenza Vaccine

Booster Vaccination Dose:

<3 years of age at time of booster vaccination: 1 x 0.25 mL

≥3 years of age at time of booster vaccination: 1 x 0.5 mL

Mode of Administration: Intramuscular injection into the deltoid region of the arm

DURATION OF TREATMENT:

In the Booster Vaccination Series a single vaccine dose was administered on Day 365 ± 14

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Not applicable

CRITERIA FOR EVALUATION:

Populations for Analysis - Booster Vaccination Series

The safety analysis included all participants who received the Booster Dose of Study Vaccine consistent with the prescribed dose for their age group. The immunogenicity analysis included all participants who received the Booster Dose, who had evaluable pre- and post-booster vaccination serology results, who did not have laboratory-confirmed flu-like illness and who had received the Study Vaccine consistent with the prescribed dose for their age group. Exclusion of a participant from the Evaluable Population for any other reason was at the discretion of the CSL Medical Monitor (e.g. use of a prohibited medication).

Immunogenicity Evaluation

Haemagglutination inhibition (HI) and single radial haemolysis (SRH) assays were performed on prebooster and post-booster vaccination serum samples obtained from the participants, and the data collected were used to determine immunogenic response according to the criteria set down in the CPMP/BWP/214/96 Note for Guidance on Harmonisation of Requirements for Influenza Vaccines for individuals aged ≥18 to <60 years of age. These criteria were applied to assess vaccine immunogenicity in a paediatric population. The immunogenicity of CSL's Inactivated Influenza Vaccine was demonstrated for each age cohort [Group A (≥6 months to <3 years) and Group B (≥3 years to <9 years)] for each of the three strains with at least one of the following criteria being met:

• More than 40% of participants in each age cohort seroconverted or demonstrated a significant increase in antihaemagglutinin antibody titre (derived from the HI or SRH assay).

• A mean geometric increase in antihaemagglutinin antibody titre (HI assay) or SRH arithmetic mean zone annulus area (AMZAA) was greater than 2.5 fold.

• More than 70% of participants in each age cohort had a post-booster vaccination antihaemagglutinin antibody titre (HI assay) greater than or equal to 40 or SRH AMZAA greater than 25 mm2.

Note: The HI assay was conducted on all three influenza strains (H1N1, H3N2 and B) contained in the vaccine, the SRH assay was only conducted on the B strain.

Safety Evaluation

The safety and tolerability of the Study Vaccine was assessed from the occurrence of solicited local and systemic AEs and unsolicited AEs. Safety measures, including medical evaluations, oral or axillary temperature, occurrence of solicited local and systemic AEs, unsolicited AEs (recorded on the Diary Card or reported during study visits), intercurrent flu-like symptoms and SAEs, were recorded and the AE data were collated and analysed.

STATISTICAL ANALYSES:

No inferential statistics were used. Statistical analyses for both immunogenicity and safety results comprised summary and descriptive statistics. Summaries were tabulated for demographic and clinical data.

RESULTS:

Safety Results:

Overall, the nature and frequency of the solicited local and systemic reactions reported following booster vaccination was as expected for the paediatric population, as identified in CSL's Inactivated Influenza Vaccine Product Information leaflet.

Pain at the vaccination site was the most commonly experienced local solicited symptom, affecting more than half of Group A and Group B participants. Fever, Rhinitis and Irritability were the most commonly reported solicited systemic symptoms following vaccination, experienced by approximately one-third of vaccinees in both age groups.

There were 225 unsolicited AEs in the Safety Population (Group A n= 72, Group B n= 153); of which most were mild to moderate in intensity and 8.9% were considered related to the Study Vaccine. At the participant level, 41.5% (n= 113) of the Safety Population experienced at least one unsolicited AE; these events were severe in intensity in 7.7% and considered related to Booster Dose in 6.6% of participants. There was one incidence of virologically-confirmed influenza illness, however, the throat swab specimen was compromised prior to testing (i.e. the sample was not properly sealed and leaked into the bag in which it was transported). No participant withdrew as a result of an AE. There were ten SAEs reported during the follow-up period between the Primary Vaccination Series Exit and the Booster Vaccination Visit. All of these were deemed not related to the Study Vaccine. Two SAEs were reported during the Booster Vaccination Series. Two Group B participants experienced Fever and Vomiting on the day of vaccination that necessitated hospitalisation. These two SAEs were unexpected in severity and were deemed to be causally related to the Study Vaccine.

At 6 months post-Booster vaccination a further 6 SAEs were reported and all events were deemed not related to the study vaccine by the Principal Investigator.

Immunogenicity Results:

When assessed using the HI assay, the Booster Dose of the Study Vaccine met all three CPMP criteria in both age groups for the H1N1 strain and met all three CPMP criteria for Group A and two of three individual CPMP criteria for Group B for the H3N2 strain. For the B strain, the Study Vaccine met all three CPMP criteria for both age groups using the SRH assay, but none of the criteria using the HI assay in Group A and two out of three individual CPMP criteria in Group B. Overall, the Booster Dose of the Study Vaccine passed the CPMP criteria for the three stains by either HI or SRH assay in both age groups.

CONCLUSIONS:

Overall, the Booster Dose of CSL's Inactivated Influenza Vaccine was safe & well tolerated in a paediatric population. The primary objective of the study was to determine the safety of a Booster Dose of CSL's Inactivated Influenza Vaccine in a paediatric population. The solicited and unsolicited AEs experienced by the study participants were as expected for a paediatric population, in terms of the nature, frequency and duration of symptoms. Pain, Redness and Swelling at the vaccination site were reported by more than 50% of participants in Group A and Group B. Similarly, Fever, Rhinitis and Irritability were the most commonly reported solicited systemic AEs following vaccination. Less than 10% of the AEs reported by the study participants were attributable to the Study Vaccine, with the majority of these being of mild or moderate intensity. Two SAEs were reported during the Booster

Phase of this study. Two participants in Group B experienced Fever and Vomiting on the day of vaccination. Both participants were hospitalised. The PI/delegate assessed these two SAEs to be causally related to the Study Vaccine. There were no withdrawals resulting from a solicited or unsolicited AE and no deaths were reported. There was one virologically-confirmed case of Influenza-Like Illness.

At 6 months post-Booster vaccination a further 6 SAEs were reported and all events were deemed not related to the study vaccine by the Principal Investigator.

The secondary objective of the study was to evaluate the immunogenicity of a Booster Dose of CSL's Inactivated Influenza Vaccine in a paediatric population according to the CPMP/BWP/214/96 Note for Guidance on Harmonisation of Requirements for Influenza Vaccine. In Group A, all three CPMP criteria (seroconversion or significant increase, fold increase in GMT and seroprotection) were met for H1N1 and H3N2 strains by the HI assay. For the B strain, the three CPMP criteria were met using the SRH assay. In Group B, all three CPMP criteria (seroconversion or significant increase, fold increase in GMT and seroprotection) were met for the H1N1 strain, whilst two of three CPMP criteria were met for the H3N2 strain. For the B strain, two of three CPMP criteria were met using the HI assay and all three were met using the SRH assay.

In conclusion, the Booster Dose of CSL's Inactivated Influenza Vaccine was generally safe, well tolerated and immunogenic for all three constituent influenza antigens in children aged >6 months to <9 years.

Date of Final Issue: 06 September 2006