# RESULTS SUMMARY

A Single Site, Open-Label Study to Evaluate the Immunogenicity and Safety of Influenza Vaccine (CSL Limited) in Healthy Adults aged ≥ 18 to < 60 years and in Healthy Older Adults aged ≥ 60 years for the 2005 Northern Hemisphere Influenza Season

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| Protocol No: | CSLCT-NHF-04-99 |
| Study Product: | Influenza Vaccine (CSL Limited) |
| Sponsor: | CSL Limited<br>45 Poplar Road<br>Parkville, Victoria 3052<br>Australia |
| Indication Studied: | Influenza Vaccine |
| Development Phase: | Phase III |
| Study Initiation Date: | 31 May 2005 (First Participant, First Visit [FPFV]) |
| Date of Early Study Termination: | Not applicable |
| Study Completion Date: | 25 June 2005 (Last Participant, Last Visit [LPLV]) |
| Report Issue Date: | Final: 29 July 2005 |
| Date of Results Summary: | 11 December 2015 |
| Good Clinical Practice (GCP) Statement: | This study was conducted in accordance with the principles of GCP CPMP/ICH/135/95 |

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| Title of Study: | A single site, open-label study to evaluate the immunogenicity and safety of Influenza Vaccine (CSL Limited) in healthy Adults aged ≥ 18 to < 60 years and in healthy Older Adults aged ≥ 60 years for the 2005 Northern Hemisphere influenza season. |
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| Study Centre(s): | A single study centre based in the United Kingdom (UK). |
| Publication (reference): | Not applicable. |
| Studied period:<br>FPFV:<br>LPLV: | Phase of development: Phase III<br>31 May 2005<br>25 June 2005 |
| Objectives: | Primary objective: To evaluate the immunogenicity of Influenza Vaccine (CSL Limited) in healthy Adults aged ≥ 18 to < 60 years and in healthy Older Adults aged ≥ 60 years of age according to the criteria of the *CPMP/BWP/214/96* guideline.<br><br>Secondary objectives: To evaluate the safety of Influenza Vaccine (CSL Limited) in healthy Adults aged ≥ 18 to < 60 years of age and in healthy Older Adults aged ≥ 60 years of age through the assessment of the frequency of Solicited local and general symptoms for 3 days following vaccination and Unsolicited adverse events (AEs) of more than 2 days duration. |
| Methods: | **Pre-study**: Participants were recruited and given a Participant Information Sheet (PIS) and appointment for Visit 1 was made.<br><br>**Visit 1 – Day of Vaccination** (Day 0) Pre-vaccination: Written informed consent was obtained, review of medical history, pregnancy status, brief medical evaluation, inclusion/exclusion criteria and oral temperature recorded, 10 mL blood sample taken for the determination of baseline (pre-vaccination) anti-haemagglutinin antibody titre, previous influenza vaccination status and history were recorded. Vaccination: Study vaccine was administered; participants were issued a 4-Day Solicited and Unsolicited AE diary card (including a local reaction measurement card) and a thermometer to record AEs and temperature on the evening of the vaccination and on every subsequent evening for the following 3 days. The participant was instructed to return the completed diary card to the PI/delegate at the end of the 4-Day period and was educated to recognise the signs/symptoms of flu-like illness and to contact the |

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| | PI/delegate if they experienced such signs/symptoms. An appointment was made for the Exit Evaluation Visit on Day 21.<br><br>**Day 7** (± 2 days): Participants who had not returned their diary card by Day 9 were contacted by telephone and were requested to do so as soon as possible. Diary cards were reviewed and missing information was clarified with the participant. All Solicited/Unsolicited AEs greater than 2 days duration and all serious adverse events (SAEs) were entered in the participants Case Report Form (CRF).<br><br>**Exit Evaluation Visit** (Day 21 ± 4 days): 10 mL blood sample taken for the determination of post-vaccination antibody titres, a brief medical evaluation and an appointment was made for the 4-6 months post-vaccination Off Study Visit.<br><br>**Off Study Visit** (31 September 2005 to 30 November 2005): Between 4 and 6 months post-vaccination, participants were to return to the study site to provide a 10 mL blood sample for the determination of post-vaccination antibody titres. The PI/delegate was to determine if the participant had experienced a flu-like illness since exiting the study.<br><br>**Intercurrent Flu-Like Illness Visit**: Participants experiencing signs/symptoms of an intercurrent flu-like illness at any time between vaccination and the Exit Evaluation Visit were asked to attend an additional visit for medical confirmation of the flu-like illness. If the symptoms were confirmed, attempts were made to isolate any virus present in the respiratory tract within 3 days following onset of symptoms. |
| Number of participants (planned and analysed): | Planned: 120 healthy participants<br>60 Adults and 60 Older Adults.<br>Analysed: 119 participants were included in the Evaluable population (60 Adult and 59 Older Adult participants) and 120 participants were included in the Safety population (60 Adults and 60 Older Adults). |
| Diagnosis and main criteria for inclusion: | Healthy male or female participants, aged ≥ 18 years, provision of written informed consent and willingness to adhere to all Protocol requirements, able to provide a sample of up to 10 mL of venous blood without undue distress/discomfort, negative pregnancy test at enrolment (female participants of child-bearing potential only) and taking/using adequate methods of contraception (oral contraception, intrauterine contraception device, depot contraceptive, abstinence, partner vasectomy and condoms with spermicide). |

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| Test product, dose and mode of administration: | Influenza Vaccine (CSL Limited) was provided as a single 0.5 mL dose containing a total of 45 µg of influenza haemagglutinin antigens (15 µg each) of the approved three strains for the Northern Hemisphere 2005/2006:<br><br>15 µg A/New Caledonia/20/99($H_1N_1$)-like strain (A/Caledonia/20/99 strain).<br>15 µg A/California/7/2004($H_3N_2$)-like strain (A/New York/55/2004 strain).<br>15 µg B/Shanghai/361/2002-like strain (B/Jiangsu/10/2003 strain).<br><br>Suspension for intramuscular or deep subcutaneous injection into the deltoid region of the arm. Where possible, the injection was administered into the arm contra-lateral to where the serology sample was obtained. |
| Duration of treatment: | The maximum time 'on-study' for an individual participant was 21 ± 4 Days from administration of the study vaccine. The maximum duration for a participant 'off-study' will be 4 to 6 months post-vaccination. |
| Reference therapy, dose and mode of administration: | No reference therapy was used in this study. |
| Criteria for evaluation: | |
| **Immunogenicity:** | Laboratory analysis: Haemagglutinin inhibition assay (HAI) and single radial haemolysis (SRH) assay. |
| **Safety:** | The assessment of the frequency of Solicited local and general symptoms for 3 days following vaccination and Unsolicited AEs of more than 2 days duration. |
| Statistical Methods: | The Evaluable population was used for the analysis of the immunogenicity data and the Safety population was used for the analysis of the safety data.<br><br>Descriptive statistics were used to present all safety and immunogenicity data.<br><br>The *CPMP/BWP/214/96* guideline provides the assessments to be considered for the determination of the immunogenicity of influenza vaccines (for each influenza virus strain, at least one of the assessments listed below were to be met):<br><br>For vaccinees aged ≥ 18 < 60 years:<br><br>• The number of seroconversions* or significant increase in anti-haemagglutinin antibody titre (haemagglutinin inhibition [HI] or SRH) should be > 40%. |

- The mean geometric increase should be > 2.5.
- The proportion of participants achieving a HI titre ≥ 40 or SRH mean zone annulus area > 25 $mm^2$ should be > 70%.

For vaccinees aged ≥ 60, the criteria were as follows:

- The number of seroconversions* or significant increase in anti-haemagglutinin antibody titre (HI or SRH) should be > 30%.
- The mean geometric increase should be > 2.0.
- The proportion or participants achieving a HI titre ≥ 40 or SRH mean zone annulus area ≥ 25 $mm^2$ should be > 60%.

*seroconversion was defined as a pre-vaccination HI titre of < 10 and a post-vaccination titre of ≥ 40. A significant increase was defined as a four-fold increase in HI titre for those with a pre-vaccination HI titre of ≥ 10.

SUMMARY - CONCLUSIONS

**IMMUNOGENICITY RESULTS:**

The *CPMP/BWP/214/96* guideline provides the assessments to be considered for determination of the immunogenicity of influenza vaccines as outlined in the statistical methods of the synopsis.

In the Adult group, the HI data for the A/New Caledonia strain met the seroconversion criteria, mean geometric increase (for both the Safety and Evaluable population) and the seroprotection criteria.

The A/New Caledonia strain in the Older Adult group met the mean geometric increase for the Safety and Evaluable population.

The HI data for the A/New York strain met the seroconversion criteria, mean geometric increase (for both the Safety and Evaluable population) and the seroprotection criteria in both Adult and Older Adult groups.

The HI data for the B/Jiangsu strain in the Adult Group met the seroconversion criteria, mean geometric increase (for both the Safety and Evaluable population) but did not meet the seroprotection criteria. However, the SRH data for the B/Jiangsu strain met the seroconversion criteria, mean geometric increase and the seroprotection criteria.

In the Older Adult group, the B/Jiangsu strain met the mean geometric increase only, but the SRH data met the seroconversion, mean geometric increase and seroprotection criteria.

**SAFETY RESULTS:**

The majority of participants did not experience any general symptoms from Day 0 to Day 3.

There were a higher number of participants experiencing local symptoms from Day 0 to Day 3 compared to general symptoms. No events were considered serious. The most common local symptom experienced for both groups was pain.

At total of 14 participants (10 Adults and 4 Older Adults) experienced flu-like symptoms between Visit 1 and the Exit Evaluation Visit. One participant (Older Adult group) had symptoms that met the criteria for flu-like illness, but did not return for the additional visit; therefore no nasal swab was taken for this participant. Two 2 Adult participants had an Intercurrent Flu-Like Illness Visit. One Adult did not have symptoms that met the criteria for flu-like illness and 1 Adult had a nasal swab taken, which was negative.

The number of participants experiencing Unsolicited AEs were: 8/60 (13.3%) Adults with 11 AEs and 8/60 (13.3%) Older Adults with 9 AEs.

The majority of Unsolicited AEs for both groups were considered unlikely to be related to the study vaccine. There were a small number of related Unsolicited AEs: 4/60 (6.7%) Adults with 5 AEs and 2/60 (3.3%) Older Adults with 2 AEs.

The majority of Unsolicited AEs overall were considered to be moderate in severity.

Overall, the most frequent Unsolicited AE was upper respiratory tract infection. Only 1 mild upper respiratory tract infection in the Older Adult group was considered to be related to the study vaccine.

Related Unsolicited AEs experienced in the Adult group were: fatigue (possibly related), rash (possibly related) and pain (definitely related) (all 3 AEs moderate in severity) along with tenderness (mild in severity and probably related). Participant 9128 who had experienced moderate fatigue, which was considered possibly related to the study vaccine also experienced a flu-like illness but did not match the flu-like illness criteria.

In the Older Adult group, related Unsolicited AEs were: upper respiratory tract infection and injection site pruritis, both mild in severity and possibly and probably related, respectively.

There were no discontinuations due to Solicited and Unsolicited AEs and no SAEs or deaths reported in this study.

**CONCLUSION:**

- A single 0.5 mL dose of the Influenza Vaccine (CSL Limited) containing 15 µg antigen of each of the strains A/New Caledonia/20/99($H_1N_1$)-like strain (A/Caledonia strain), A/California/7/2004($H_3N_2$)-like strain (A/New York strain), B/Shanghai/361/2002-like strain (B/Jiangsu strain) in both the Adult and Older Adult populations met the efficacy criteria specified in the *CPMP/BWP/214/96* guideline.
- The Influenza Vaccine (CSL Limited) was seen to be safe and well tolerated in both the Adult and Older Adult populations in this study.

Date of the report: Final (29 July 2005).

Date of Results Summary: 11 December 2015

# ADDENDUM TO THE ORIGINAL CLINICAL STUDY REPORT

A Single Site, Open-Label Study to Evaluate the Immunogenicity and Safety of Influenza Vaccine (CSL Limited) in Healthy Adults aged ≥ 18 to < 60 years and in Healthy Older Adults aged ≥ 60 years for the 2005 Northern Hemisphere Influenza Season

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| Protocol No: | CSLCT-NHF-04-99 |
| Study Product: | Influenza Vaccine (CSL Limited) |
| Sponsor: | CSL Limited<br>45 Poplar Road<br>Parkville, Victoria 3052<br>Australia |
| Indication Studied: | Influenza Vaccine |
| Development Phase: | Phase III |
| Off Study Initiation Date: | 10 November 2005 (First Participant First Visit [FPFV]) |
| Date of Early Study Termination: | Not applicable |
| Off Study Completion Date: | 18 November 2005 (Last Participant Last Visit [LPLV]) |
| Report Issue Date: | Final: 23 February 2006 |
| Date of Results Summary: | 11 December 2015 |
| Good Clinical Practice (GCP) Statement: | This study was conducted in accordance with the principles of GCP CPMP/ICH/135/95 |

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| Title of Study: | A single site, open-label study to evaluate the immunogenicity and safety of Influenza Vaccine (CSL Limited) in healthy Adults aged ≥ 18 to < 60 years and in healthy Older Adults aged ≥ 60 years for the 2005 Northern Hemisphere influenza season. |
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| Study Centre(s): | A single study centre based in the United Kingdom (UK). |
| Publication (reference): | Not applicable. |
| Studied period:<br>4 to 6 Month 'Off-Study' Post-Vaccination Visit:<br>FPFV:<br>LPLV: | Phase of development: Phase III<br><br><br>10 November 2005<br>18 November 2005 |
| Primary Study Objectives: | Primary objective: To evaluate the immunogenicity of Influenza Vaccine (CSL Limited) in healthy Adults aged ≥ 18 to < 60 years and in healthy Older Adults aged ≥ 60 years of age according to the criteria of the *CPMP/BWP/214/96* Note for Guidance.<br><br>Secondary objectives: To evaluate the safety of Influenza Vaccine (CSL Limited) in healthy Adults aged ≥ 18 to < 60 years of age and in healthy Older Adults aged ≥ 60 years of age through the assessment of the frequency of Solicited local and general symptoms for 3 days following vaccination and Unsolicited adverse events (AEs) of more than 2 days duration. |
| Methods: | There was a maximum of 4 study visits in all: 3 were on-site (Visit 1 – Day of Vaccination, Exit Evaluation Visit and Off Study Visit) and 1 visit was an on-site Intercurrent Flu-Like Illness Visit (if applicable). This addendum presents the data for the Off Study Visit only.<br><br>**Off Study Visit:** Between 4 and 6 months post-vaccination, participants returned to the study site to provide a 10 mL blood sample for the determination of post-vaccination antibody titres. The PI/delegate also determined if the participant had experienced a flu-like illness since exiting the study. |
| Number of participants for the Off Study Visit (planned and analysed): | 120 healthy participants were enrolled: 60 Adult and 60 Older Adult participants.<br><br>101 participants returned for the Off Study Visit and were included in the Follow-Up Population: 47 Adult and 54 Older Adult participants. A total of 96 participants were included in the Follow-Up Evaluable Population: 45 Adult and 51 Older Adult participants. |
| Diagnosis and main criteria for inclusion: | For further details, refer to the full Results Summary. |
| Test product, dose and mode of administration: | Influenza Vaccine (CSL Limited) was provided as a single 0.5 mL dose containing a total of 45 µg of influenza |

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| | haemagglutinin antigens (15 µg each) of the approved three strains for the Northern Hemisphere 2005/2006:<br><br>15 µg A/New Caledonia/20/99($H_1N_1$)-like strain (A/Caledonia/20/99 strain).<br>15 µg A/California/7/2004($H_3N_2$)-like strain (A/New York/55/2004 strain).<br>15 µg B/Shanghai/361/2002-like strain (B/Jiangsu/10/2003 strain).<br><br>Suspension for intramuscular or deep subcutaneous injection into the deltoid region of the arm. Where possible, the injection was administered into the arm contra-lateral to where the serology sample was obtained. |
| Duration of treatment: | The maximum time 'on-study' for an individual participant was 21 ± 4 days from administration of the study vaccine. The maximum duration for a participant 'off study' was 4 to 6 months post-vaccination, which consisted of one on-site study visit (1 day). |
| Reference therapy, dose and mode of administration: | No reference therapy was used in this study. |
| Criteria for evaluation:<br>**Immunogenicity:**<br><br>**Occurrence of Influenza-Like Illness:** | <br>Laboratory analysis: Haemagglutinin Inhibition Assay (HAI) and Single Radial Haemolysis (SRH) assay.<br><br>The occurrence of any influenza-like illness since the study exit. |
| Statistical Methods: | The immunogenicity and the occurrence of influenza-like illness analysis were performed using the Follow-Up Evaluable Population. The Follow-Up Population was used for the analysis of the influenza-like illness data only. Note: There was a change to the title of this population (the SAP Addendum refers to this population as the Follow-Up Safety Population).<br><br>Descriptive statistics were used to present all immunogenicity and occurrence of influenza-like illness data.<br><br>The following statistics were performed.<br><br>For vaccinees aged ≥ 18 < 60 years:<br><br>• The number of seroconversions* or significant increase** in antihaemagglutinin antibody titre (haemagglutinin inhibition [HI] or SRH) should be > 40%.<br><br>• The mean geometric increase should be > 2.5.<br><br>• The proportion of participants achieving a HI titre ≥ 40 or SRH mean zone annulus area > 25 $mm^2$ should be > 70% (seroprotection rate).<br><br>For vaccinees aged ≥ 60 years:<br><br>• The number of seroconversions* or significant increase** in antihaemagglutinin antibody titre (HI |

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| | or SRH) should be > 30%.<br>• The mean geometric increase should be > 2.0.<br>• The proportion or participants achieving a HI titre ≥ 40 or SRH mean zone annulus area ≥ 25 $mm^2$ should be > 60% (seroprotection rate).<br>* Seroconversion was defined as a pre-vaccination HI titre of < 10 (undetectable) and an increase in serum HI to ≥ 40 post-vaccination (follow-up).<br>** Significant increase was defined as the number and percentage of participants with serum HI titre ≥ 10 pre-vaccination and a four-fold antibody titre increase post-vaccination (follow-up). |

SUMMARY – CONCLUSIONS

**IMMUNOGENICITY RESULTS:**

For the 4 to 6 month Off Study Visit, the post-vaccination seroprotection rate (the number of participants having a HI titre ≥ 40 or zone annulus area > 25 $mm^2$ for Adults and ≥ 25 $mm^2$ for Older Adults) was of particular interest.

In the Adult group, the number of participants who maintained seroprotective antibody titres at 4 to 6 months post-vaccination were: 86.7% participants for the A/New York ($H_3N_2$) strain, 57.8% participants for the A/Caledonia ($H_1N_1$) strain and 40.0% participants for the B/Jiangsu (B strain) strain.

In the Older Adult group, the number of participants who maintained seroprotective antibody titres at 4 to 6 months post-vaccination were: 80.4% participants for the A/New York ($H_3N_2$) strain, 45.1% participants for the A/Caledonia ($H_1N_1$) strain and 37.3% participants for the B/Jiangsu (B strain) strain.

A total of 44.4% Adult participants and 47.1% Older Adult participants maintained seroprotection for the B/Jiangsu (B strain) strain (SRH zone annulus area) at 4 to 6 months post-vaccination.

**OCCURRENCE OF INFLUENZA-LIKE ILLNESS:**

No participants experienced influenza-like symptoms since exiting the study.

**CONCLUSION:**

- Adults maintaining a persistent seroprotective HI antibody titre at 4 to 6 months post-vaccination were: 86.7% for the A/New York ($H_3N_2$) strain, 57.8% for the A/Caledonia ($H_1N_1$) strain and 40.0% for the B/Jiangsu (B strain) strain (44.4% for the SRH zone annulus area [B strain]).
- Older Adults maintaining a persistent seroprotective HI antibody titre at 4 to 6 months post-vaccination were: 80.4% for the A/New York ($H_3N_2$) strain, 45.1% for the A/Caledonia ($H_1N_1$) strain and 37.3% for the B/Jiangsu (B strain) strain (47.1% for the SRH zone annulus area [B strain]).

Date of the report: Final (23 February 2006)

Date of Results Summary: 11 December 2015