# RESULT SUMMARY

A Single Centre, Open-Label Study to Evaluate the Immunogenicity and Safety of Enzira® vaccine in Healthy 'Adults' aged ≥ 18 to < 60 years and in Healthy 'Older Adults' aged ≥ 60 years for the 2007/2008 Northern Hemisphere Influenza Season

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| Protocol No: | CSLCT-NHF-06-30 |
| EudraCT No: | 2007-001465-14 |
| Study Product: | Enzira® vaccine 2007/2008 (Influenza Vaccine, CSL Limited) |
| Sponsor: | CSL Limited |
| Address: | 45 Poplar Road, Parkville, Victoria 3052, Australia |

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| Indication Studied: | Prophylaxis of Influenza |
| Development Phase: | Phase IV |
| Study Initiation Date: | 29 May 2007 (First Participant First Visit [FPFV]) |
| Date of Early Study Termination: | Not applicable |
| Study Completion Date: | 22 June 2007 (Last Participant Last Visit [LPLV]) |
| Report Issue Date: | Final 29 July 2007 |
| Date of Results Summary: | 10 December 2015 |

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| Good Clinical Practice (GCP) Statement: | This trial was conducted in accordance with the principles of GCP CPMP/ICH/135/95 |

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| Title of Study: | A Single Centre, Open-Label Study to Evaluate the Immunogenicity and Safety of Enzira® vaccine in Healthy 'Adults' aged ≥ 18 to < 60 years and in Healthy 'Older Adults' aged ≥ 60 years for the 2007/2008 Northern Hemisphere Influenza Season. |
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| Study Centre: | One (1) study site based in the United Kingdom (UK). |
| Publication (reference): | Not applicable |
| Studied period (years):<br>FPFV<br>LPLV | Phase of development: Phase IV<br>29 May 2007<br>22 June 2007 |
| Objectives: | Primary objective:<br>To evaluate the immunogenicity of Enzira® vaccine in healthy 'Adults' aged ≥ 18 to < 60 years of age and in healthy 'Older Adults' aged ≥ 60 years of age according to the criteria of the *CPMP/BWP/214/96 Note for Guidance on Harmonisation of Requirements for Influenza Vaccines*.<br>Secondary objectives:<br>To evaluate the safety of Enzira® vaccine in healthy 'Adults' aged ≥ 18 to < 60 years of age and in healthy 'Older Adults' aged ≥ 60 years of age through:<br>• The assessment of the frequency of solicited local reactions and general symptoms for 3 days following vaccination.<br>• The assessment of unsolicited adverse events (AEs) of more than 2 days duration. |
| Methods: | **Pre-study:** Participants were recruited and given a Participant Information Sheet (PIS) and an appointment for Visit 1 was made.<br>**Visit 1** - Day of Vaccination (Day 0) Pre-vaccination: written informed consent was obtained. A medical history was taken (including a review of concomitant medications, influenza history and influenza vaccine status), brief medical evaluation (including physical examination, if clinically indicated), oral temperature was taken, inclusion/exclusion criteria were reviewed and a 20 mL blood sample taken for the determination of baseline (pre-vaccination) anti-haemagglutinin antibody titre.<br>Vaccination: A single dose of Study Vaccine was administered (0.5 mL of Enzira® vaccine 2007/2008) into the deltoid region of the arm.<br>Post-Vaccination: Participants were observed for 30 minutes in case of any rare anaphylactic reaction. Participants were issued a 4-day Solicited and Unsolicited AE diary card (including local reaction measurement card) and a digital thermometer and were instructed to complete the card and take their oral temperature on the |

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| | evening of vaccination (Day 0) and every subsequent evening for the following 3 days. Participants were instructed to return the completed diary card to the Principal Investigator (PI)/delegate at the end of the 4-day period and were educated to recognise signs/symptoms of flu-like illness. They were instructed to contact the 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 7 (± 2 days) were contacted by telephone and were requested to do so as soon as possible. For participants who had returned their diary card, a review of the diary cards was performed and missing information was clarified with the participant via telephone. All solicited AEs, unsolicited AEs (of more than two days duration) and Serious Adverse Events (SAEs) were entered in the participant's Case Report Form (CRF).<br><br>**Exit Evaluation** (Day 21 ± 4 days): A 20 mL blood sample was taken for the determination of post-vaccination antibody titres. An assessment of any SAEs that had occurred since Visit 1 and a brief medical evaluation (including a physical examination, if clinically indicated) were performed.<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 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 by obtaining nasal swab specimens within 3 days, following symptom onset. |
| Number of participants (planned and analysed): | Planned: 120 participants (60 'Adults' and 60 'Older Adults').<br><br>Analysed: Evaluable Population 120 participants (60 'Adults' and 60 'Older Adults').<br><br>Safety Population 120 participants (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 20 mL of venous blood without undue distress/discomfort on two occasions (pre- and post-vaccination), negative pregnancy test at enrolment (for female participants of child-bearing potential only) and taking/using adequate methods of contraception during the study period (oral contraception, intrauterine contraceptive device, depot contraceptive, abstinence, partner vasectomy and condoms with spermicide). |

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| Test product, dose and mode of administration: | Enzira® vaccine 2007/2008, CSL Biotherapies GmbH was provided as a single 0.5 mL dose containing a total of 45 µg of influenza haemagglutinin antigens (15 µg of each of the following 3 strains), which complied with the World Health Organisation (WHO) recommendation (Northern Hemisphere) and European Union (EU) decision for the 2007/2008 season:<br>• A/Solomon Islands/3/2006 ($H_1N_1$-like) strain.<br>• A/Wisconsin/67/2005 ($H_3N_2$-like) strain.<br>• B/Malaysia/2506/2004-like strain.<br>Administration: Intramuscular or subcutaneous injection into the deltoid region of the arm. Where possible, the Study Vaccine was administered into the arm contra-lateral to where the pre-vaccination serology sample was obtained. |
| Duration of treatment: | The maximum time on the study for an individual participant was 21 ± 4 days from the administration of the Study Vaccine. |
| Reference therapy, dose and mode of administration: | Not applicable. |
| Criteria for evaluation: | |
| Immunogenicity: | Laboratory analysis: Haemagglutination Inhibition Assay (HAI) and Influenza Viral Isolation Assay as required. |
| Safety: | Assessment of the frequency of solicited local reactions and general symptoms as well as unsolicited AEs (of more than 2 days duration) for 3 days, following vaccination and the frequency of SAEs occurring during the study period (21 ± 4 days post-vaccination). |
| 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>Descriptive statistics were used to present all safety and immunogenicity results.<br>The *CPMP/BWP/214/96 Note for Guidance on Harmonisation of Requirements for Influenza Vaccines* provides the assessments to be considered for determination of the immunogenicity of influenza vaccines.<br>For vaccinees aged ≥ 18 to < 60 years, the criteria are as follows:<br>• The proportion of participants achieving seroconversion or significant increase* in anti-haemagglutinin antibody titre (HI) should be > 40% of the evaluable population.<br>• The mean geometric fold increase should be > 2.5.<br>• The proportion of participants achieving a HI titre |

≥ 40 should be > 70% of the evaluable population.

For vaccinees aged ≥ 60 years, the criteria are as follows:

- The proportion of participants achieving seroconversion or significant increase* in anti-haemagglutinin antibody titre (HI) should be > 30% of the evaluable population.
- The mean geometric fold increase should be > 2.0.
- The proportion of participants achieving a HI titre ≥ 40 should be > 60% of the evaluable population.

* Seroconversion or significant increase was defined as a post-vaccination titre of ≥ 40 for those with a pre-vaccination HI titre of < 10 and a fourfold or greater increase in HI titre for those with a pre-vaccination HI titre of ≥ 10.

According to the guidance document, for each influenza virus strain included in the vaccine, at least one of the criteria listed above should be met.

SUMMARY – CONCLUSIONS

**IMMUNOGENICITY RESULTS:**

With respect to immunogenicity data, the *CPMP/BWP/214/96 Note for Guidance* suggests that at least one of the three serological criteria be met for each influenza strain in both the Adult and Older Adult groups.

In both the Adult and Older Adult groups, the HI data for the $H_1N_1$ (A/Solomon Islands/3/2006-like) strain, the $H_3N_2$ (A/Wisconsin/67/2005-like) strain and the B/Malaysia/2506/2004-like strain met all three serological criteria (seroconversion and/or significant increase, geometric fold increase and seroprotection).

Therefore the Enzira® vaccine 2007/2008 meets the *CPMP/BWP/214/96* criteria for both the Adult and Older Adult study population.

Secondary Exploratory Analysis

Exploratory subgroup analyses were conducted to explore the impact of participant level factors potentially impacting on post-vaccination serum HI antibody results. These included subgroups defined by previous influenza vaccination history and pre-vaccination serum HI antibody levels.

Descriptive subgroup comparisons against the standard *CPMP/BWP/214/96* immunogenicity endpoints indicate that previous influenza vaccination history and pre-vaccination serum HI antibody levels do appear to impact on post-vaccination serum HI antibody endpoints. These impacts vary according to the influenza strain and immunogenicity endpoint. The number of participants in some of the subgroups is very small so the differences are difficult to interpret.

**SAFETY RESULTS:**

The majority of Adult (91.7%) and Older Adult (93.3%) participants in this study did not experience general symptoms following a single dose of Enzira® vaccine 2007/2008 (0.5 mL). No participants had an elevated temperature (above 38°C) for 24 hours or longer. Local symptoms reported were as expected for an Inactivated Influenza Vaccine. The most frequent local symptoms at the site of vaccination were pain and erythema. No

participants had induration of greater than 50 mm diameter persisting for more than 3 days. A small number of participants in each group reported ecchymosis. These local reactions were considered to be causally related to Study Vaccine. No events were considered serious.

There were no occurrences of flu-like illness during this study.

Overall, the incidence of unsolicited AEs was low with no participants in the Older Adult group experiencing unsolicited AEs. Two participants in the Adult group experienced three unsolicited AEs. All three unsolicited AEs were mild in severity with two possibly related (sneezing, local swelling of the armpit) and one not causally related (vessel puncture site haematoma) to Study Vaccine.

There were no discontinuations due to solicited or unsolicited AEs in this study and there were no deaths, SAEs, or other significant AEs.

**CONCLUSION:**

- A single dose of 0.5 mL Enzira® vaccine 2007/2008, containing 15 µg of antigen of each of the strains, A/Solomon Islands/3/2006 ($H_1N_1$-like) strain, 15 µg A/Wisconsin/67/2005 ($H_3N_2$-like) strain, 15 µg B/Malaysia/2506/2004-like strain, met the immunogenicity criteria specified in the *CPMP/BWP/214/96* guideline in both the Adult and Older Adult population.
- Enzira® vaccine 2007/2008 administered as a single dose (0.5 mL) was safe and well tolerated in the Adult and Older Adult study populations.

Date of the report: Final 29 July 2007

Date of Result Summary: 10 December 2015