# RESULTS SUMMARY

A Single Site, Open-Label Study to Evaluate the Immunogenicity and Safety of Enzira® in Healthy 'Adults' aged ≥ 18 to < 60 years and in Healthy 'Older Adults' aged ≥ 60 years for the 2006/2007 Northern Hemisphere Influenza Season

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| Protocol No: | CSLCT-NHF-05-13 |
| EudraCT No: | 2006-002068-25 |
| Study Product: | Enzira® 2006/2007 |
| Sponsor: | CSL Limited<br>45 Poplar Road, Parkville, Victoria 3052, Australia |
| Indication Studied: | Influenza Vaccine |
| Development Phase: | Phase IV |
| Study Initiation Date: | 25 May 2006 (initiation) 30 May 2006 (First Participant First Visit [FPFV]) |
| Date of Early Study Termination: | Not applicable |
| Study Completion Date: | 23 June 2006 (Last Participant Last Visit [LPLV]) |
| Report Issue Date: | Final 31 July 2006 |
| Date of Results Summary: | 09 Dec 2015 |
| 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 Site, Open-Label Study to Evaluate the Immunogenicity and Safety of Enzira® in Healthy 'Adults' aged ≥ 18 to < 60 years and in Healthy 'Older Adults' aged ≥ 60 years for the 2006/2007 Northern Hemisphere Influenza Season. |
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| Study Site(s): | One (1) clinical site, based in the United Kingdom (UK). |
| Publication (reference): | Not applicable. |
| Studied period (years):<br>FPFV<br>LPLV | Phase of development: Phase IV<br>30 May 2006<br>23 June 2006 |
| 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 review of concomitant medications, influenza history and influenza vaccine status), brief medical evaluation (including physical examination, if clinically indicated), oral temperature taken, inclusion/exclusion criteria 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 2006/2007).<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) and a digital |

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| | thermometer and were instructed to complete the card and take their oral temperature on the evening of vaccination 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. A review of the diary cards was performed and missing information was clarified with the participant. All Solicited and Unsolicited AEs/Serious Adverse Events (SAEs) were entered in the participants Case Report Form (CRF).<br><br>**Exit Evaluation Day** (Day 21 ± 4 days): A 20 mL blood sample was taken for the determination of post-vaccination antibody titres, an assessment of any SAEs and a brief medical evaluation was 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 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 by obtaining nasal swab specimens within 3 days, following symptom onset. |
| Number of patients (planned and analysed): | Planned: Up to 120 participants (60 'Adults' and 60 'Older Adults').<br><br>Analysed: Evaluable Population 119 participants (59 'Adults' and 60 'Older Adults').<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, 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). |
| Test product, dose and mode of administration: | Enzira® vaccine 2006/2007, ZLB Pharma 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 |

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| | World Health Organisation (WHO) recommendation (Northern Hemisphere) and European Union (EU) decision for the 2006/2007 season:<br>• 15 µg A/New Caledonia/20/99($H_1N_1$)-like strain<br>• 15 µg A/Wisconsin/67/2005($H_3N_2$)-like strain<br>• 15 µg B/Malaysia/2506/2004-like strain<br>Administration: Suspension for 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 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:** | Haemagglutinin Inhibition Assay (HI), Single Radial Haemolysis (SRH) Assay and Viral Isolation Assay as required. |
| **Safety:** | Assessment of the frequency of Solicited local and general symptoms for 3 days and Unsolicited AEs (of more than 2 days duration), 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>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 number of seroconversions* or significant increase in anti-haemagglutinin antibody titre (HI or SRH) should be > 40%;<br>• The mean geometric increase should be > 2.5;<br>• The proportion of participants achieving a HI titre ≥ 40 or SRH mean zone annulus area > 25 $mm^2$ should be > 70%.<br>For vaccinees aged ≥ 60 years, the criteria are as follows:<br>• 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 of participants achieving a HI titre $\geq$ 40 or SRH mean zone annulus area $\geq$ 25 $mm^2$ should be > 60%.

*Seroconversion is defined as a pre-vaccination HI titre of < 10 and a post-vaccination titre of $\geq$ 40. A significant increase is defined as a fourfold increase in HI titre for those with a pre-vaccination HI titre of $\geq$10.

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

Additional SRH assays were conducted for the B strain only for informational purposes.

SUMMARY - CONCLUSIONS

**IMMUNOGENICITY RESULTS:**

With respect to Immunogenicity data, the *CPMP/BWP/214/96 Note for Guidance on Harmonisation of Requirements for Influenza Vaccines* 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 the Adult group, the HI data for the $H_1N_1$ (A/New Caledonia/20/99)-like strain met the mean geometric fold increase and seroprotection criteria. The HI data for the $H_3N_2$ (A/Wisconsin/67/2005)-like strain and the B/Malaysia/2506/2004-like strain met the criteria for seroconversion and/or significant increase, geometric fold increase and seroprotection.

Therefore the Enzira® 2006/2007 vaccine meets the *CPMP/BWP/214/96* immunogenicity criteria for the Adult study population.

In the Older Adult group, the HI data for the $H_3N_2$ (A/Wisconsin/67/2005)-like strain met the criteria for geometric fold increase and seroprotection. The HI data for the B/Malaysia/2506/2004-like strain met the criteria for seroconversion and/or significant increase, geometric fold increase and seroprotection, and the SRH data met all three criteria.

In the Older Adult group, the HI data for the $H_1N_1$ (A/New Caledonia/20/99)-like strain did not meet the suggested criteria. However, there are a number of factors which may have an impact upon post-vaccination antibody titre response and these must be considered. The potential factors are, age, influenza infection, pre-vaccination titre level and previous vaccination history. For this study in the Older Adult group, due to the fact that 100% of participants received influenza vaccination the previous year (a much higher proportion than in previous recent studies), it was deemed pertinent that the immunogenicity results should also be analysed with the pre-vaccination serological status of the participant in mind. Therefore, the response to vaccination in participants, not considered to be seroprotected (HI titre < 40) prior to vaccination with Enzira® 2006/2007, was also assessed. When considering Older Adult participants without evidence of pre-vaccination seroprotection, the CPMP criterion for geometric fold increase for the $H_1N_1$ (A/New Caledonia/20/99)-like strain was met (geometric fold increase = 2.19). This observation was based on a group size of 43 Older Adult participants. The CPMP suggested group size is 50 participants.

**SAFETY RESULTS:**

The majority of study participants did not experience any general symptoms from Day 0

to Day 3. The most common general symptoms were shivering and malaise reported between Day 0 to Day 3. The events were considered either 'unlikely related', 'possibly related' or 'probably related' to Study Vaccine. There were no participants who had an elevated temperature or fever (above 38°C) for 24 hours or longer.

The most common local symptoms were injection site pain and erythema. A small number of participants in each group reported ecchymosis and induration greater than 50 mm diameter. These local reactions were considered 'definitely related' to Study Vaccine.

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

Overall, the incidence of unsolicited AEs was minimal with all AEs being either unlikely to be related or not related to Study Vaccine. The most frequent AEs were of upper respiratory tract infection. The majority of AEs were mild or moderate in intensity.

There were no discontinuations due to AEs, no SAEs, significant AEs or deaths reported during this study.

**CONCLUSION:**

- A single dose of 0.5 mL Enzira® 2006/2007 vaccine, containing 15 µg of antigen of each of the strains, A/New Caledonia/20/99($H_1N_1$)-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 the Adult population
- A single dose of 0.5 mL Enzira® 2006/2007 vaccine, containing 15 µg of antigen of each of the strains, A/New Caledonia/20/99($H_1N_1$)-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 the Older Adult population for the A/Wisconsin/67/2005($H_3N_2$)-like strain and the B/Malaysia/2506/2004-like strain, and marginally failed to meet the criteria for the A/New Caledonia/20/99($H_1N_1$)-like strain.
    - When considering Older Adult participants without evidence of pre-vaccination seroprotection, the *CPMP/BWP/214/96* guideline criterion for geometric fold increase for the $H_1N_1$ (A/New Caledonia/20/99)-like strain was met (geometric fold increase = 2.19). This observation was based on a group size of 43 Older Adult participants. The CPMP suggested group size is 50 participants.
- Enzira® 2006/2007 vaccine administered as a single dose (0.5 mL) is safe and well tolerated in the Adult and Older Adult study populations.

Date of the report: Final 31 July 2006

Date of Results Summary: 09 December 2015