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 2008/2009 Northern Hemisphere Influenza Season

Protocol No:	CSLCT-NHF-08-55
EudraCT No:	2008-005324-93
Study Product:	Enzira® vaccine (Influenza Vaccine, CSL Limited)
Sponsor:	CSL Limited
Contact Details:	45 Poplar Road, Parkville Victoria 3052, Australia
Indication Studied:	Prophylaxis of influenza
Development Phase:	Phase IV
Study Initiation Date:	27 September 2008
Study Completion Date:	19 October 2008
Report Issue Date:	15 December 2008
Date of Result Summary	08 December 2015
Good Clinical Practice (GCP) Statement:	This trial was conducted in accordance with the principles of GCP CPMP/ICH/135/95

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 2008/2009 Northern Hemisphere Influenza Season
Study centre:	One UK based site
Publication (reference):	Not applicable
Phase of development:	IV
Studied period (years):	First Participant First Visit (FPFV): 27 September 2008 Last Participant Last Visit (LPLV): 19 October 2008
Objectives:	
Primary:	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.
Secondary:	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: • The assessment of the frequency of solicited local reactions and general symptoms for 3 days following vaccination. • 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. **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 17 mL blood sample taken for the determination of baseline (pre-vaccination) anti haemagglutinin antibody titre. Vaccination: A single dose of Study Vaccine was administered (0.5 mL of Enzira® vaccine 2008/2009) into the deltoid region of the arm. 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 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. **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 source data files and the Case Report Form (CRF). **Exit Evaluation** (Day 21 ± 4 days): Between Day 17 and Day 25, participants were to present for a 17 mL blood sample, for the determination of post-vaccination antibody titres. An assessment of any AEs of more than two days duration that had occurred since Visit 1 and a brief medical evaluation (including a physical examination, if clinically indicated) were performed. **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:	120 participants (60 'Adults', 60 'Older Adults') Evaluable Population: 120 participants (60 'Adults', 60 'Older Adults').

Analysed:	Safety Population: 120 participants (60 'Adults', 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 17 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).
Test product: Dose and mode of administration:	Enzira® vaccine 2008/2009, 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 2008/2009 season: • A/Brisbane/59/2007 (H1N1)-like strain • A/Brisbane/10/2007 (H3N2)-like strain • B/Florida/4/2006-like strain. 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:	Single dose; 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) at Day 0 and Day 21 ± 4, influenza viral isolation assay as required. Single Radial Haemolysis (SRH) would be performed if required.
Safety:	Assessment of the frequency of solicited local reactions and general symptoms for 3 days, following vaccination. Assessment of the frequency of unsolicited AEs of more than 2 days duration, for 3 days following vaccination.
Statistical Methods:	The Evaluable Population was used for the analysis of immunogenicity data and the Safety Population was used for the analysis of the safety data. Descriptive statistics were used to present all safety and immunogenicity results. 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. For vaccinees aged ≥ 18 to < 60 years, the criteria are as follows: • The proportion of participants achieving seroconversion or significant increase* in anti-haemagglutinin antibody titre (HI or SRH) should be > 40% of the evaluable population. • The geometric mean fold 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% 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 or SRH) should be > 30% of the evaluable population. • The geometric mean fold increase should be > 2.0. • The proportion of participants achieving a HI titre ≥ 40 or SRH mean zone annulus area ≥ 25 mm^2 should be > 60% of the evaluable population. *Seroconversion or significant increase was defined as achieving a post-vaccination titre of ≥ 40 for those with a pre-vaccination HI titre of < 10 (seroconversion) and a fourfold or greater increase in HI titre for those with a pre-vaccination HI titre of ≥ 10. For SRH seroconversion or significant increase was defined as a post-vaccination area ≥ 25 mm^2 if pre-vaccination SRH was negative, i.e., area ≤ 4 mm^2 or an increase in area of at least 50%. 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 **EFFICACY 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/Brisbane /59/2007 like) strain, and the H_3N_2 (A/Brisbane/10/2007 like) strain met all of the three serological criteria (seroconversion and/or significant increase, geometric mean fold increase and seroprotection). With respect to the B (B/Florida/4/2006-like) strain two out of the three serological criteria were met in the Adult group and one of the criteria in the Older Adult group. Therefore the Enzira® vaccine 2008/2009 meets the CPMP/BWP/214/96 criteria for both the Adult and Older Adult study population with respect to the H_1N_1, H_3N_2 and B strains.

Exploratory subgroup analyses were conducted to assess 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.

The results of these subgroup analyses were consistent with the primary immunogenicity outcomes, and it is unlikely that previous influenza vaccination history and pre-vaccination serum HI antibody levels had significant impact on post-vaccination serum HI antibody results.

SAFETY RESULTS:

The majority of participants in both the Adult (86.7%) and Older Adult (90.0%) group did not experience any general symptoms following a single dose of Enzira® vaccine 2008/2009 (0.5 mL). One participant in the Adult group (1/60 [1.7%]) and one participant in the Older Adult group (1/60 [1.7%]) had a temperature of 38.0-39.0°C for 24 hours or longer. These events were considered possibly and probably related to Study Vaccine, respectively. Local symptoms reported were as expected for an Inactivated Influenza Vaccine. The most frequent local symptoms were erythema and pain. Three participants in the Adult group (3 events) and 2 participants in the Older Adult group (2 events) had an induration larger than 50 mm.

There were no participants in the Adult group and three participants in the Older Adult group who had sign/symptoms of flu-like illness between Visit 1 and the Exit Visit. These participants did not return for an additional visit.

Overall, the incidence of unsolicited AEs was low, with most of the AEs being assessed as mild in intensity. Two participants experienced AEs of severe intensity; however these events were considered unrelated 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 Enzira® vaccine 2008/2009, containing 15 µg of antigen of each of the strains, A/Brisbane/59/2007 (H_1N_1 –like) strain, A/Brisbane/10/2007 (H_3N_2-like) strain and B/Florida/4/2006-like strain met the immunogenicity criteria specified in the CPMP/BWP/214/96 guideline in both the Adult and Older Adult population.
- Enzira® vaccine 2008/2009 vaccine administered as a single dose (0.5 mL) was safe and well tolerated in both the Adult and Older Adult study population.

Date of the report: 15 December 2008

Date of the Result Summary: 08 December 2015