RESULTS SUMMARY

A Phase IV, Randomised, Observer-Blind, Comparator-Controlled, Single-Centre Study to Evaluate the Immunogenicity, Safety and Tolerability of CSL Influenza Vaccine (Enzira®) (2006/2007) in Healthy Older Adults aged ≥ 65 years.

Protocol No:	CSLCT-NHF-05-15
EudraCT No:	2006-004354-24
Study Product:	Enzira® 2006/2007
Sponsor:	CSL Limited
Name & Contact Details:	45 Poplar Road, Parkville, Victoria 3052, Australia
Indication Studied:	Influenza Prophylaxis
Development Phase:	Phase IV
Study Initiation Date:	27 October 2006
Study Completion Date:	29 December 2006
Report Issue Date:	21 March 2007
Date of Results Summary:	10 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 Phase IV, Randomised, Observer-Blind, Comparator-Controlled, Single-Centre Study to Evaluate the Immunogenicity, Safety and Tolerability of CSL Influenza Vaccine (Enzira®) (2006/2007) in Healthy Older Adults aged ≥ 65 years.
Study Centre(s):	One (1) clinical site based in the United Kingdom (UK).
Publication (reference):	Not applicable.
Studied period (years): FPFV LPLV	Phase of development: Phase IV 27 October 2006 29 December 2006
Objectives:	Primary Objective • To demonstrate that vaccination with CSL Influenza Vaccine (Enzira®) (2006/2007) produced an immune response sufficient to meet the Committee for Medicinal Products for Human Use (CPMP) criteria for Older Adults of > 30% seroconversion and > 60% seroprotection. Secondary Objectives • To demonstrate that CSL Influenza Vaccine (Enzira®) (2006/2007) was no more reactogenic than GlaxoSmithKline Influenza Vaccine (Fluarix® or Influsplit®) 2006/2007 in Healthy Older Adults aged ≥ 65 years. • To demonstrate that vaccination with CSL Influenza Vaccine (Enzira®) (2006/2007) produced an immune response in Healthy Older Adults aged ≥ 65 years sufficient to meet the criteria of the *CPMP/BWP/214/96 Note for Guidance on Harmonisation of Requirements for Influenza Vaccines* in Older Adults.
Methods:	**Pre-study:** Participants were recruited through the Independent Ethics Committee (IEC) approved advertisements and provided with 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**,** prior to any study related procedures being undertaken. A review of medical history taken (including concomitant medications), previous influenza history and vaccination status including any adverse reactions to previous vaccinations, brief medical evaluation (including a physical examination, if clinically indicated), oral temperature taken, inclusion/exclusion criteria reviewed and a 20 mL blood sample was taken for the determination of a baseline (pre-vaccination)

	anti-haemagglutinin antibody titre. Vaccination – Since the two Study Vaccines differed in appearance an unblinded Investigator/medically qualified delegate administered a single 0.5 mL dose of Study Vaccine into the deltoid region of the arm, by intramuscular or deep subcutaneous (SC) injection. Where possible the injection was administered into the arm contralateral to where the pre-vaccination blood sample was obtained. Post-vaccination – Participants were observed for 30 minutes post-vaccination and were issued a 5-Day Solicited Adverse Event (AE) diary card and a 21-day Unsolicited AE diary card. Participants were also provided with a local reaction measurement card and digital thermometer and were instructed to record their temperature and complete the 5-day Solicited AE diary card on the evening of the vaccination (Day 0) and on every subsequent evening for the following 4 days. Participants were instructed to return the completed 5-day diary card to the Principal Investigator (PI)/delegate at the end of the 5-day period and to return the 21-day unsolicited AE diary card at their Exit Visit. Participants were educated to recognise the signs/symptoms of flu-like illness and asked to contact the PI/delegate immediately if they experienced such signs/symptoms. An appointment was made for the participant to return for the Exit Evaluation Visit on Day 21. **Day 8 (± 2 days):** Participants who had not returned their 5-day solicited AE diary card by Day 10 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 participant's Case Report Form (CRF). **Exit Evaluation (Day 21 + 4 days):** Between Day 21 and Day 25 a second 20 mL blood sample was taken for determination of post-vaccination Haemagglutination Inhibition (HI) antibody titres; determination of whether any AEs had occurred and a brief medical evaluation was performed by a blinded PI or delegate (including a physical examination, if clinically indicated). **Intercurrent Flu-Like Illness:** Participants experiencing signs/symptoms of an intercurrent flu-like illness (refer to section 9.5.1 for criteria) at any time between vaccination and 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 virus present in the respiratory tract by obtaining nasal wash/swab specimens within three days following the onset of symptoms.
Number of patients	Planned: 400 participants

(planned and analysed):	Participants were randomised in a 3:1 ratio to receive CSL Influenza Vaccine (Enzira®) 2006/2007 or GlaxoSmithKline Influenza Vaccine (Fluarix® or Influsplit®) 2006/2007. The recruitment of participants ceased on 08 December 2006 because of the difficulty in recruiting Older Adults who had not already been vaccinated with the 2006/2007 Northern Hemisphere Influenza Vaccine. Analysed: Evaluable Population 274 participants (206 Enzira® 2006/2007 group participants, 68 Influsplit® 2006/2007 vaccine group participants). Safety Population 275 participants (206 Enzira® 2006/2007 group participants, 69 Influsplit® 2006/2007 vaccine group participants).
Diagnosis and main criteria for inclusion:	Participants were included in the study provided they met the following criteria: • Healthy males or females, aged ≥ 65 years at the time of providing informed consent. • Provision of written informed consent to participate in the study and willingness to adhere to all Protocol requirements. • Were in good health, as determined by medical history and physical examination where indicated. • Were able to understand and comply with planned study procedures.
Test product, dose and mode of administration:	Active Ingredient: Split virion, inactivated influenza virus, propagated in hen's eggs, containing antigens (HA) of the following strains: • 15 µg A/New Caledonia/20/99(H1N1)-like virus (A/New Caledonia/20/99 IVR-116); • 15 µg A/Wisconsin/67/2005 (H3N2)-like virus (A/Hiroshima/52/2005 IVR-142); • 15 µg B/Malaysia/2506/2004-like virus (B/Malaysia/2506/2004). A total of 45 µg HA. Quantity/Pre-filled Syringe: 0.5 mL of thiomersal-free liquid formulation containing 45 µg of influenza HA antigens. Route of Administration: Intramuscular or deep subcutaneous injection only. Dose Form: Suspension for injection in pre-filled syringe. Manufacturer: CSL Limited
Duration of treatment:	The maximum time on the study for an individual participant was 21 + 4 days from the administration of the vaccine.
Reference therapy, dose	Active Ingredient:

and mode of administration:	Split virion, inactivated influenza virus, containing antigens (HA) of the following strains: • 15 µg A/New Caledonia/20/99 (H1N1)-like strain: (A/New Caledonia/20/99 IVR-116). • 15 µg A/Wisconsin/67/2005 (H3N2)-like strain: (A/Wisconsin/67/2005). • 15 µg B/Malaysia/2506/2004 -like strain: (B/Malaysia/2506/2004). A total of 45 µg HA. Quantity/Pre-filled Syringe: 0.5 mL suspension for injection in pre-filled syringe (Type I glass) with a plunger stopper (butyl) with or without needles – pack of 1, 10 or 20. Route of Administration: Intramuscular or deep subcutaneous injection only. Dose Form: Suspension for injection in pre-filled syringe. Manufacturer: GSK
Criteria for evaluation: **Immunogenicity:** **Safety:**	• For each strain, the proportion of study participants achieving seroconversion should be greater than 30%, and the proportion achieving HI titres ≥ 1:40 should be greater than 60%. This was assessed via the 97.5% one-sided binomial confidence limit for the respective proportion. Assessment of the frequency of Solicited systemic and local reactions and Unsolicited AEs. • Frequency of Solicited local reactions for 5 days following vaccination (Day 0 to Day 4): pain, tenderness, erythema, swelling, induration and ecchymosis at the vaccination site. • Frequency of Solicited general symptoms for 5 days following vaccination: fever, headache, malaise, myalgia, chills, nausea and vomiting. • Frequency of Unsolicited AEs for 21 + 4 days following vaccination. *Duration of unsolicited AEs has been clarified by a file note.* • Frequency of SAEs occurring during the Study period (21 + 4 days post-vaccination).
Statistical Methods:	Immunogenicity: The primary endpoints for immunogenicity were the co-primary endpoints of seroprotection rate and seroconversion rate. Seroprotection is defined as a minimum post vaccination haemagglutination inhibition (HI) titre of 1:40. Seroconversion is defined as an increase in HI antibody titre of at least 4-fold, with a minimum post vaccination HI titre of 1:40. For each strain, the proportion of study participants

vaccinated with CSL influenza Vaccine (Enzira®) (2006/2007) achieving seroconversion should be greater than 30%, and the proportion achieving HI titres ≥ 1:40 should be greater than 60%.

The secondary endpoint was to assess the immune response of CSL Influenza Vaccine (Enzira®) (2006/2007) according to the criteria of the *CPMP/BWP/214/96 Note for Guidance on Harmonisation of Requirements for Influenza Vaccines* for Older Adults.

A formal comparison of the immunogenicity results of the study vaccine and the comparator vaccine was not planned, however, summaries of immune responses were to be used to assess whether general response patterns exhibited in both groups.

Safety:

Although the frequency of induration, erythema, vaccination site pain, tenderness and ecchymosis at the vaccination site were assessed, the primary endpoint for safety was the proportion of participants who experience the following solicited local or systemic reactions during the 4 days following vaccination:

Local Reactions

- Induration (hard lump)
- Swelling
- Erythema (redness)
- Vaccination site pain
- Tenderness
- Ecchymosis (bruising)

Systemic Reactions

- Fever
- Headache
- Malaise (feeling unwell)
- Myalgia (muscle aches)
- Chills/shivering
- Nausea
- Vomiting

The numbers and proportions of participants experiencing these reactions were presented along with exact 95% confidence intervals for each treatment group. The differences in percentages CSL Influenza Vaccine (Enzira®) (2006/2007) – and GlaxoSmithKline Influenza Vaccine (GlaxoSmithKline Influenza Vaccine (Fluarix® or Influsplit® 2006/2007) were presented along with exact one-sided 97.5% upper confidence limits. CSL Influenza Vaccine (Enzira®) (2006/2007) would be considered no more reactogenic than GlaxoSmithKline Influenza Vaccine

	(Fluarix® or Influsplit®) 2006/2007 if this upper confidence limit is ≤10%. *Power* Assuming that CSL Influenza Vaccine (Enzira®) 2006/2007 and GlaxoSmithKline Influenza Vaccine (Fluarix® or Influsplit®) 2006/2007 had equivalent reactogenicity, and the true rate was <15%, then with sample sizes of 300 and 100 for the CSL Influenza Vaccine (Enzira®) and GlaxoSmithKline Influenza Vaccine (Fluarix® or Influsplit®) arms, respectively, this test of non-inferiority had at least 84% power.

SUMMARY - CONCLUSIONS

IMMUNOGENICITY RESULTS:

The Co-primary immunogenicity endpoints of seroprotection and seroconversion were met. The proportion of participants achieving seroconversion were found to be greater than 30%, and the proportion achieving HI titres ≥ 1:40 was greater than 60%.

With respect to secondary endpoint, the *CPMP/BWP/214/96 Note for Guidance on Harmonisation of Requirements for Influenza Vaccines* for Older Adults provides the assessments and criteria for determination of the immunogenicity of influenza vaccines. According to the guidance document, for each influenza virus strain, at least one of the criteria should be met.

In the Enzira® 2006/2007 group the HI data for the H1N1 (A/New Caledonia/20/99-like) virus strain, H3N2 (A/Wisconsin/67/2005-like) virus and B (B/Malaysia/2506/2004-like) virus strain met the CPMP criteria for seroconversion and/or significant increase, geometric fold increase and seroprotection. Co-primary immunogenicity endpoints of seroprotection and seroconversion were met. Therefore, the Enzira® 2006/2007 Vaccine meets the *CPMP/BWP/214/96 Note for Guidance on Harmonisation of Requirements for Influenza Vaccines* for an Older Adult population.

In the Influsplit® 2006/2007 group the HI data for the H1N1(A/New Caledonia/20/99-like) virus strain, H3N2 (A/Wisconsin/67/2005-like) virus and B (B/Malaysia/2506/2004-like) virus strain met the CPMP criteria for seroconversion and/or significant increase, geometric fold increase and seroprotection.

SAFETY RESULTS:

Overall, majority of the AEs reported were of mild to moderate severity. There were no occurrences of intercurrent flu-like illness during this study.

Systemic reactions were as expected and the frequency was comparable between the two groups. The most common systemic reactions were headache, malaise, myalgia and chills. The incidence of pain, tenderness, erythema/redness, induration/hard lump and swelling after administration of the Study Vaccine was higher in the Enzira® 2006/2007 vaccine group compared to the Influsplit® 2006/2007. The overall incidence of Unsolicited AEs in this study was comparable between the two groups and majority of AEs were considered to be mild or moderate in intensity.

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

CONCLUSION:

- Co-primary immunogenicity endpoints of seroprotection and seroconversion were met. 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(H1N1)-like virus; A/Wisconsin/67/2005 (H3N2)-like virus; 15 µg B/Malaysia/2506/2004-like virus strain, met the immunogenicity criteria specified in the *CPMP/BWP/214/96 Note for Guidance on Harmonisation of Requirements for Influenza Vaccines* guideline for an Older Adult population.

- Safety of Enzira® 2006/2007 vaccine has been established. Solicited systemic reactions and Unsolicited AEs maintained a pattern consistent with the vaccine's established safety profile and were comparable with the Influsplit® 2006/2007 group.

  However, the current trial results showed an increased incidence of local site reactions after use of Enzira® 2006/2007 vaccine compared to Influsplit® 2006/2007.

Date of the report: Final Audited dated 21 March 2007

Date of Results Summary: 10 December 2015