RESULTS SUMMARY

A Randomised, Observer-Blind, Single-Centre Study to Evaluate the Safety, Tolerability and Immunogenicity of Enzira™ 2005/2006 Compared to Mutagrip® 2005/2006 in Healthy Adults Aged ≥ 18 to < 60 Years and in Healthy Older Adults Aged ≥ 60 Years

Protocol No:	CSLCT-NHF-05-11
Study Product:	Enzira™ 2005/2006
Sponsor:	CSL Limited 45 Poplar Road, Parkville, Victoria 3052, Australia
Indication Studied:	Influenza Vaccine
Development Phase:	Phase IV
Study Initiation Date:	06 October 2005 (First Participant First Visit [FPFV])
Date of Early Study Termination:	Not applicable
Study Completion Date:	17 November 2005 (Last Participant Last Visit [LPLV])
Report Issue Date:	19 January 2006 (Final)
Date of Results Summary:	08 December 2015
Good Clinical Practice (GCP) Statement:	This study was conducted in accordance with the principles of GCP CPMP/ICH/135/95

Title of Study:	A Randomised, Observer-Blind, Single-Centre Study to Evaluate the Safety, Tolerability and Immunogenicity of Enzira™ 2005/2006 Compared to Mutagrip® 2005/2006 in Healthy Adults Aged ≥ 18 to < 60 Years and in Healthy Older Adults Aged ≥ 60 Years.
Study Centre(s):	A single study centre based in the United Kingdom (UK).
Publication (reference):	Not applicable.
Studied period (years): FPFV LPLV	Phase of development: Phase IV 06 October 2005 17 November 2005
Objectives:	Primary objective: • To demonstrate that the immune response following vaccination with Enzira™ 2005/2006 in healthy Adults aged ≥ 18 to < 60 years and in healthy Older Adults aged ≥ 60 years meets the criteria of the *CPMP/BWP/214/96* Note for Guidance. Secondary objectives: • To demonstrate that vaccination with Enzira™ 2005/2006 elicits a non-inferior immune response compared to vaccination with Mutagrip® 2005/2006 in healthy Adults aged ≥ 18 to < 60 years and in healthy Older Adults aged ≥ 60 years according to the criteria of the *CPMP/BWP/214/96* Note for Guidance. • To demonstrate that Enzira™ 2005/2006 is no more reactogenic in healthy Adults aged ≥ 18 to < 60 years and in healthy Older Adults aged ≥ 60 years than Mutagrip® 2005/2006 according to the criteria of the *CPMP/BWP/214/96* Note for Guidance.
Methods:	**Pre-Study:** Participants were recruited and given a Participant Information Sheet (PIS) and an appointment for Visit 1 was made. **Visit 1** - Vaccine Administration (Day 0) Pre-Vaccination: Written informed consent was obtained, review of medical history taken (including concomitant medications, influenza history and influenza vaccination status), brief medical evaluation (including a 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. Vaccination: A single dose of Study Vaccine was administered (0.5 mL of either Enzira™ 2005/2006 or

	Mutagrip® 2005/2006). Participants were issued a 4-Day Solicited and Unsolicited Adverse Event (AE) diary card (including a local reaction measurement card) and a digital thermometer and were instructed to complete the card and take their oral 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 Principal Investigator (PI)/delegate at the end of the 4-Day period and was educated to recognise signs/symptoms of flu-like illness and to contact the PI/delegate if they experienced such signs/symptoms. An appointment was made for the participant to return for the Exit Evaluation Visit on Day 21. **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. 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). **Exit Evaluation Visit, 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. **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 virus present in the respiratory tract by obtaining nasal wash/swab specimens within 3 days following onset of symptoms.
Number of participants (planned and analysed):	Planned: 400 healthy participants (Cohort A - Adults, n=200 [Enzira™ 2005/2006 n=100, Mutagrip® 2005/2006 n=100] and Cohort B - Older Adults, n=200 [Enzira™ 2005/2006 n=100, Mutagrip® 2005/2006 n=100]). Analysed: 206 participants were included in the Enzira™ 2005/2006 Evaluable and Safety Population (Adults n=102 and Older Adults n=104) and 200 participants were included in the Mutagrip® 2005/2006 Evaluable and Safety Population (Adults n=102 and Older Adults n=98).
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™ 2005/2006, 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 3 strains), which complied with the World Health Organisation (WHO) recommendation (Northern Hemisphere) and European Union (EU) decision for the 2005/2006 season: • 15 µg A/New Caledonia/20/99(H_1N_1) like strain (A/Caledonia/20/99 IVR-116 strain) • 15 µg A/California/7/2004(H_3N_2) like strain (A/New York/55/2004 [NYMC X-157] strain) • 15 µg B/Shanghai/361/2002 like strain (B/Jiangsu/10/2003 strain). Presentation: 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 the administration of the Study Vaccine.
Reference therapy, dose and mode of administration:	Mutagrip® 2005/2006 (Sanofi Pasteur MSD 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 3 strains), which complied with the WHO recommendation (Northern Hemisphere) and EU decision for the 2005/2006 season: • 15 µg A/New Caledonia/20/99(H_1N_1) like strain (A/Caledonia/20/99 IVR-116 strain) • 15 µg A/California/7/2004(H_3N_2) like strain (A/New York/55/2004 [NYMC X-157] strain) • 15 µg B/Shanghai/361/2002 like strain (B/Jiangsu/10/2003 strain) Presentation: 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.
Criteria for evaluation:	
Immunogenicity:	Laboratory analysis: Haemagglutinin inhibition assay (HAI), single radial haemolysis (SRH) assay and viral isolation as required.
Safety:	Assessment of the frequency of Solicited local and general symptoms and Unsolicited AEs for 4 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. The *CPMP/BWP/214/96* Note for Guidance provides the age specific criteria for haemagglutinin inhibition (HI) serology results for each of the 3 strains in each population cohort. The Study Vaccines were considered to be immunogenic for a particular strain if at least one of the following was observed for that strain: • The proportion of vaccinees with seroconversion (i.e. pre-vaccination HI titre of < 10 and a post-vaccination titre ≥ 40 or pre-vaccination titre of ≥ 10 and ≥ 4 fold increase in HI titre) was > 40% for participants aged ≥ 18 to < 60 years and > 30% for participants aged ≥ 60 years. • The mean geometric increase was > 2.5 for participants aged ≥ 18 to < 60 years and > 2.0 for participants aged ≥ 60 years. • The proportion of participants achieving a HI titre ≥ 40 (seroprotection rate) was > 70% for participants aged ≥ 18 to < 60 years and > 60% for participants aged ≥ 60 years. Enzira™ 2005/2006 was to be considered non-inferior to Mutagrip® 2005/2006 if the upper confidence interval (CI) for the difference (Mutagrip® 2005/2006 - Enzira™ 2005/2006) in the seroprotection rate and the seroconversion/significant increase rate did not exceed 20% and if the ratio of the geometric mean increase in HI titres did not exceed 2.0. Enzira™ 2005/2006 was to be considered no more reactogenic than Mutagrip® 2005/2006 if the upper CI for the difference (Enzira™ 2005/2006 - Mutagrip® 2005/2006) for the proportion of subjects experiencing local and systemic reactions did not exceed 15%. Additional SRH assays for the B strain only were conducted for informational purposes only.
SUMMARY – CONCLUSIONS IMMUNOGENICITY RESULTS: The *CPMP/BWP/214/96* Note for Guidance provides the assessments to be considered for determination of the immunogenicity of influenza vaccines as outlined in the statistical methods of the synopsis. For the Enzira™ 2005/2006 Study Vaccine, the HI data for the Adult and Older Adult groups met the *CPMP/BWP/214/96* Note for Guidance criteria for the three strains (H_1N_1, H_3N_2 and B strain). The SRH data for the B strain met the seroconversion criteria and the mean geometric increase, but not the seroprotection criteria. For the Mutagrip® 2005/2006 Study Vaccine, the HI data for the Adult group met the *CPMP/BWP/214/96* Note for Guidance criteria for the three strains (H_1N_1, H_3N_2 and	

B strain). In the Older Adult group, the HI data for the H_3N_2 strain the *CPMP/BWP/214/96* Note for Guidance criteria. However, the H_1N_1 and B strain met the seroconversion and mean geometric increase criteria, but not the seroprotection criteria. The SRH data for the B strain met the seroconversion and the mean geometric increase criteria, but not the seroprotection criteria.

Therefore, both Study Vaccines satisfied the *CPMP/BWP/214/96* Note for Guidance criteria for immunogenicity.

Enzira™ 2005/2006 also met the non-inferiority criteria for all three strains for both the Adult and Older Adult groups, for the rates of seroconversion or significant increase, ratios of the geometric increase in titres and the seroprotection rates.

SAFETY RESULTS:

The majority of participants in both vaccine groups did not experience any general symptoms from Day 0 to Day 3. The most frequent local symptoms reported in both groups were pain and erythema. The reactogenicity of Enzira™ 2005/2006 was also similar to that of Mutagrip® 2005/2006, with an upper CI of the comparisons being ≤ 15%. Therefore Enzira™ 2005/2006 was shown to be non-inferior to Mutagrip® 2005/2006 in terms of reactogenicity.

The overall incidence of Unsolicited AEs was very low in this study, with more events reported by participants receiving Mutagrip® 2005/2006. A total of 4/206 (1.9%) participants in the Enzira™ 2005/2006 group compared to 9/200 (4.5%) participants in the Mutagrip® 2005/2006 group experienced Unsolicited AEs. There were 2 related Unsolicited AEs experienced in the Enzira™ 2005/2006 group; 1 participant experienced moderate myalgia and the other participant experienced a moderate headache. There were 4 related Unsolicited AEs in the Mutagrip® 2005/2006 group (2 Adult and 2 Older Adult participants experiencing 1 event each). In the Adult group there were reports of: a mild injection site reaction and mild sneezing; in the Older Adult group there were reports of mild injection site pain and right mild joint stiffness.

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

Both vaccines were therefore safe and well-tolerated in both Adults and Older Adults.

CONCLUSIONS:

- Both Enzira™ 2005/2006 and Mutagrip® 2005/2006 met the immunogenicity criteria specified in the *CPMP/BWP/214/96* Note for Guidance in both the Adult (< 60 years) and Older Adult (≥ 60 years) group, thus satisfying the Primary Objective.
- The immunogenicity of Enzira™ 2005/2006 was non-inferior to that of Mutagrip® 2005/2006 for any of the three strains in both the Adult (< 60 years) and Older Adult (≥ 60 years) group, thus satisfying the first Secondary Objective.
- The Enzira™ 2005/2006 Study Vaccine was no more reactogenic than Mutagrip® 2005/2006 in either age group, thus satisfying the second Secondary Objective.
- Both Study Vaccines were safe and well tolerated.

Date of the report: 19 January 2006 (Final).

Date of Results Summary: 08 December 2015