RESULT SUMMARY

A Phase II, Double-Blind, Randomised, Controlled, Multi-Centre Study to Evaluate the Immunogenicity, Safety and Tolerability of Three Formulations of CSL412 in Adults (≥ 18 to ≤ 45 years) and Older Adults (≥ 60 years).

Protocol Number:	CSLCT-IIV-06-27
EudraCT No:	2007-000272-16
Study Product:	CSL412 (Influenza ISCOMATRIX® Vaccine)
Indication:	Prophylaxis of Influenza
Sponsor:	CSL Limited 45 Poplar Road, Parkville, Victoria 3052, Australia
Development Phase:	Phase II
Date of First Enrolment:	27 Apr 2007 (First Participant First Visit)
Date of Last Participant Completed (Active Study Period):	30 Sep 2007
Date of Result Summary:	09-Mar-2016 This Study was performed in compliance with Good Clinical Practice (ICH-GCP) guidelines

Title of Study:	A Phase II, Double-Blind, Randomised, Controlled, Multi-Centre Study to Evaluate the Immunogenicity, Safety and Tolerability of Three Formulations of CSL412 in Adults (≥ 18 to ≤ 45 years) and Older Adults (≥ 60 years).
Study Sites:	Eight centres in the United Kingdom (UK).
Publication (reference):	Not applicable
Phase of development:	Phase II
Active Study Period First Participant First Visit: Last Participant Last Visit: Licensed Influenza Vaccination (LIV) Study Period First LIV: Last LIV: SAE Follow-up Period:	 27 Apr 2007 30 Sep 2007 03 Oct 2007 16 Jan 2008 Day 180 + 14 days Post Vaccine Administration

Objectives:	Primary Objectives • To evaluate the immunogenicity of CSL412 in Older Adults (aged ≥ 60 years) against the immunogenicity criteria of the *CPMP/BWP/214/96 Note for Guidance on Harmonisation of Requirements for Influenza Vaccines*. • To evaluate the safety and tolerability of CSL412 as compared to active comparator vaccine. Secondary Objective • To assess the safety and tolerability of CSL412 in terms of solicited injection site and systemic adverse events (AEs), unsolicited AEs, and serious adverse events (SAEs). Exploratory Objectives • To compare the T cell response in Older Adults vaccinated with CSL412 to the T cell response in Adults and Older Adults vaccinated with unadjuvanted trivalent inactivated influenza vaccine. • To compare the T cell response in Older Adults vaccinated with CSL412 to the T cell response in Adults vaccinated with CSL412.
Methods:	**Visit 1:** Day -21 to Day -1 (Screening Visit) - Written informed consent was obtained, a review of medical history (including concomitant medications and vaccination history) was taken, brief medical evaluation, including a physical examination if clinically indicated, review of Inclusion/Exclusion criteria, measurement and recording of participant's temperature and vital signs, collection of a 13 mL blood sample for baseline hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) assessments and biochemistry and haematology assessments, and collection of a urine sample for urinalysis (and a urine pregnancy test for female participants of child-bearing potential).

Methods (continued):	**Visit 2:** Day 0 - Pre-Vaccination: Confirmation of continuing eligibility following screening visit, including review of results for baseline HBV, HCV, HIV assessments, biochemistry, haematology and urinalysis; review of concomitant medications, brief medical evaluation (including a physical examination if clinically indicated), measurement and recording of temperature and vital signs, urine pregnancy test for female participants of child-bearing potential; and collection of 66 mL blood sample for baseline immunogenicity assessments. Participants who completed all assessments and fulfilled the eligibility criteria were eligible for vaccination. Eligible participants were randomised according to the randomisation schedule for their assigned cohort. Cohorts A and B were randomised in a 1:1:1:1 ratio to Influenza Vaccine (Enzira® Vaccine): Influenza Vaccine + 30 µg ISCOMATRIX® adjuvant: Influenza Vaccine + 60 µg ISCOMATRIX® adjuvant: Influenza Vaccine + 120 µg ISCOMATRIX® adjuvant. Cohorts C and D were randomised in a 1:1 ratio to Influenza Vaccine (Enzira® Vaccine): Influenza Vaccine + 120 µg ISCOMATRIX® adjuvant. Vaccination: The Study Vaccine was administered by intramuscular injection into the deltoid region of the arm, preferably in the contra-lateral arm to that used for the blood draw. Post-Vaccination: Post-vaccination observation (30 minutes) in the event of an SAE or an anaphylactic reaction. Participants were issued with a 7-Day Solicited AE Diary card and a 30-Day Unsolicited Adverse Event (UAE) Diary Card (including an injection site adverse event measurement card). The 7-Day Solicited AE Diary Card was completed on the day of vaccination and for the following 6 days (total of 7 days). The 30-Day UAE Diary card was completed on the day of vaccination and for the following 29 days (total of 30 days). Participants were provided with a digital thermometer and instructed to record their oral temperature at the same time each evening, in addition to completing the diary cards (participants in Cohort D had their temperature measured tympanically instead of orally throughout the Study). Participants were instructed to return the completed 7-Day Solicited AE Diary Card to the Principal Investigator (PI)/delegate at the Day 7 + 3 visit (Visit 3). Participants were educated to recognise the signs/symptoms of a flu-like illness and instructed to contact the PI/delegate immediately if they experienced such signs/symptoms during the Active Study Period. An appointment was made for each participant to return for their third visit on Day 7 + 3. Note: Due to the difficulty some participants in Long-Term Care may have had in reading and completing a diary card, applicable participants in Cohort D had their Diary Card questions completed by the Investigator or delegate each day during the AE collection period, immediately after verbal confirmation of the absence/presence of symptoms. Staff were trained to ask the participant about AEs in a non-leading manner. **Day 1 - 3**: The site contacted participants in Cohorts A, B and C by phone to ensure they were completing their diary cards. **Visit 3**: Day 7 + 3: Review of 7-Day Solicited AE Diary card. Review of 30-Day UAE Diary Card. The diary card was returned to the participant with instructions to continue completion of the card until Day 30, and to bring the card to the Day 30 + 5 visit (Visit 4). Assessment of the occurrence of SAEs, review of concomitant medications, and a brief medical evaluation (including a physical examination, if clinically indicated). A 13 mL blood sample was collected for safety biochemistry and haematology assessments and a 56 mL blood sample was collected for immunogenicity assessments. Participants were reminded to contact the PI/delegate immediately if they experienced signs/symptoms of a flu-like illness. **Visit 4**: Day 30 + 5 Active Study Period Exit Visit: Review of 30-Day UAE Diary Card, brief medical evaluation (including a physical examination if clinically indicated), assessment of the occurrence of SAEs, review of

concomitant medications, collection of 13 mL blood sample for safety biochemistry and haematology assessments, collection of 58 mL blood sample for immunogenicity assessments, and collection of urine sample for urinalysis.

Participants who were indicated to receive influenza vaccine in the 2007/2008 Northern Hemisphere influenza season were invited to receive licensed, unadjuvanted trivalent inactivated influenza vaccine at the commencement of the 2007/2008 influenza vaccination season when vaccine became commercially available (Visit 5).

Intercurrent flu-like illness visit (Active Study Period only): Participants experiencing signs/symptoms of an Intercurrent flu-like illness at any time between Day 0 and the Active Study Period Exit Visit (Day 30 + 5) were asked to attend an additional visit within 3 days of the onset of the symptoms for medical confirmation of the flu-like illness. If the symptoms of influenza were confirmed at this visit, attempts were made to isolate virus present in the respiratory tract by obtaining nasal swab/wash specimens in order to determine if the participants have been infected with the circulating strains of influenza.

Active Study Period SAE Follow-Up: Day 180 + 14 days Post Study Vaccine Administration: The site contacted by phone those participants who had not received licensed Northern Hemisphere influenza vaccine in 2007/2008 and asked about the occurrence of SAEs, and documented whether the participants had received any other investigational products or any other influenza vaccines since the administration of the Study Vaccine. Participants who returned to the Study Sites for revaccination with licensed influenza vaccine within this 6 month follow-up period were also asked about the occurrence of SAEs and receipt of any other investigational products or any other influenza vaccines since the administration of the Study Vaccine.

Visit 5: Licensed Influenza Vaccination (LIV) Visit - Pre-Vaccination: Confirmation that the participant had not already received 2007/2008 licensed influenza vaccine, brief medical evaluation (including a physical examination if clinically indicated), review of concomitant medications, measurement and recording of temperature and vital signs and assessment of the occurrence of SAEs since Visit 4.

Vaccination: Vaccines were administered according to instructions provided on the vaccine's Technical Leaflet.

Post-Vaccination: 30 minute post-vaccination observation in the event of an anaphylactic reaction;

Participants were issued with a 7-Day Solicited AE Diary card (including an injection site AE measurement card) and a 30-Day UAE Diary Card. The 7-Day Solicited AE Diary Card was to be completed on the day of vaccination and for the following 6 days (total of 7 days). The 30-Day UAE Diary Card was to be completed on the day of vaccination and for the following 29 days (total of 30 days). Participants in Cohorts A, B and C were provided with a digital thermometer and instructed to record their oral temperature at the same time each evening, in addition to completing the diary cards. Participants in Cohort D had their temperature measured tympanically instead of orally throughout the LIV Study Period. The sites contacted participants in Cohorts A, B and C by phone 1 to 3 days after Visit 5 to ensure they were completing their diary cards. Participants were instructed to return their 7 Day Solicited AE Diary Card and 30 Day UAE Diary Card to the PI/delegate by post. All participants in Cohort D (residents of Long-Term Care Facilities) had their diary card questions completed by the Investigator or an appropriately qualified and trained delegate on each day during the AE collection period, immediately after verbal confirmation of the absence / presence of symptoms. Staff were trained to ask the participant about AEs in a non-leading manner.

LIV SAE Follow-Up: 180 + 14 days Post Licensed Influenza Vaccine Administration - The site contacted participants by phone to ask about the

	occurrence of SAEs.
Number of participants (planned and analysed): Number of participants (planned and analysed) continued:	Planned: 720 (four age/population cohorts with two or four treatment allocations):

	Enzira® Influenza Vaccine (n)	Influenza Vaccine + 30 µg IMX* (n)	Influenza Vaccine + 60 µg IMX* (n)	Influenza Vaccine + 120 µg IMX* (n)
Cohort A: Adults ≥18 to ≤45 yrs	60	60	60	60
Cohort B: Older Adults ≥60 to <75 yrs	60	60	60	60
Cohort C: Older Adults ≥75 yrs	60	–	–	60
Cohort D: Older Adults ≥60 yrs in Long-Term Care Facilities	60	–	–	60

***** ISCOMATRIX® adjuvant

Analysed: A total of 612 participants were enrolled into the Study and included in the Safety Population.

There were 609/612 participants who fulfilled the criteria that defined the Evaluable Population.

There were 570/612 participants who fulfilled the criteria that defined the Per Protocol population.

Diagnosis and main criteria for inclusion:	To be eligible for study entry all participants had to satisfy the following criteria: All Cohorts Provision of written informed consent to participate in the Study and willingness to adhere to all Protocol requirements prior to any study procedures. Ability to provide a pre-vaccination venous blood sample of up to 66 mL without undue distress/discomfort. Participants were not to have donated blood within the 3 months prior to Screening. Healthy Adult Cohort: Cohort A: Additional Inclusion Criteria Healthy males or females, aged ≥ 18 to ≤ 45 years at the time of provision of informed consent. Negative urine pregnancy test at enrolment before receiving Study Vaccine (female participants of childbearing potential only [defined as not surgically sterilised or less than one year post-menopausal]). Females at risk of becoming pregnant or males at risk of causing pregnancy during the Active Study Period were to, in the opinion of the PI/delegate, be taking/using at least one adequate method of contraception (defined as: oral contraception, intrauterine contraceptive device, depot contraceptive, abstinence, partner vasectomy, or condoms with spermicide). Older Adult Cohort ≥ 60 to < 75 years: Cohort B: Additional Inclusion Criteria Community dwelling males or females, aged ≥ 60 and < 75 years at the time of provision of informed consent. Older Adult Cohort ≥ 75 years: Cohort C: Additional Inclusion Criteria Community dwelling males or females, aged ≥ 75 years at the time of provision of informed consent. Older Adult Long-term Care Facility Cohort: Cohort D: Additional Inclusion Criteria Males or females, aged ≥ 60 years at the time of provision of informed consent, resident in Long-Term Care Facility (providing some degree of assisted care).
Test product, dose and mode of administration, batch number:	The investigational agents were three formulations of CSL412 (adjuvanted vaccine), each containing three influenza virus strains consistent with the recommendation of the World Health Organisation (WHO) for the 2006/2007 Northern Hemisphere influenza season. Participants received 0.5 mL of Study Vaccine (one of three formulations containing different doses of adjuvant). The three formulations containing adjuvant were: • CSL412 Formulation 1: contained 45 µg of influenza haemagglutinin antigens (15 µg of each of the three influenza virus strains), and 30 µg of ISCOMATRIX® adjuvant. • CSL412 Formulation 2: contained 45 µg of influenza haemagglutinin antigens (15 µg of each of the three influenza virus strains), and 60 µg of ISCOMATRIX® adjuvant. • CSL412 Formulation 3: contained 45 µg of influenza haemagglutinin antigens (15 µg of each of the three influenza virus strains), and 120 µg of ISCOMATRIX® adjuvant. Participants were administered a single 0.5 mL dose of Study Vaccine by intramuscular injection in the deltoid region of the arm on the day of vaccination (Day 0). Where possible, the vaccine was administered into the contra-lateral arm from where the blood sample was drawn.
Duration of treatment:	Active Study Period: 30 + 5 days Active Study Period 6 month SAE Follow-up: 180 + 14 days post-

	vaccination. LIV administration (Visit 5) LIV Safety Follow-up: 180 + 14 days following administration of licensed influenza vaccine for those participants who received licensed influenza vaccine in the 2007/2008 Northern Hemisphere influenza season.
Reference therapy, dose and mode of administration, batch number:	The comparator vaccine was CSL Biotherapies' licensed Trivalent Inactivated Influenza Vaccine (Enzira® Vaccine), containing 2006/2007 Northern Hemisphere influenza vaccine strains. Participants were administered a single 0.5 mL dose of Study Vaccine by intramuscular injection in the deltoid region of the arm on the day of vaccination (Day 0). Where possible, the vaccine was administered into the contra-lateral arm from where the blood sample was drawn.
Criteria for evaluation Immunogenicity: Safety:	Haemagglutination Inhibition (HI) assay, QuantiFERON®-CMI assay, intracellular cytokine staining (ICS) assay, and IL-10 enzyme immunoassay (EIA). Assessment of injection site AEs and systemic solicited symptoms on the day of vaccination and for 6 days post-vaccination, UAEs on the day of vaccination and for 29 days post-vaccination, and SAEs for 6 months post-vaccination with Study Vaccine and, if applicable, for 6 months post revaccination with 2007/2008 licensed influenza vaccine.
Statistical Methods:	<u>Analysis for primary endpoints (serum HI antibody)</u> Immunogenicity analyses were carried out separately for each influenza strain contained within the Study Vaccines. The *CPMP immunogenicity criteria* were tabulated by treatment group and cohort. Immunogenicity responses for Cohort A participants were assessed against the *CPMP immunogenicity criteria* for adults aged between 18 and 60 years, and the remaining cohorts (B, C and D) were assessed against the criteria for older adult populations aged ≥ 60 years. These statistics were also analysed on all cohorts combined using appropriate regression models (linear or logistic) to assess their relationship to adjuvant dose, and age, and applying covariate adjustments for sex, health status, pre-vaccination titres and previous vaccination history. <u>Analysis for primary safety endpoints (fever, ulceration, abscess or necrosis)</u> The number and percentage of participants experiencing Study Vaccine-associated Grade 3 or higher fever, or Study Vaccine-associated vaccination site ulceration, abscess or necrosis were tabulated by Study Vaccine and cohort for the Active Study Period and the LIV Study Period. <u>Analysis for secondary endpoint (safety)</u> The number and percentage of participants experiencing injection site AEs and systemic solicited symptoms, and unsolicited AEs was tabulated by Study Vaccine and cohort for the Active Study Period and the LIV Study Period. Details of any SAEs which occurred during the 6 month period following vaccination were listed by individual. <u>Analysis for exploratory endpoints (T cell responses)</u> T cell-mediated immune responses were assessed using the QuantiFERON®-CMI (QFN) assay and IL-10 enzyme immunoassay (EIA) on samples taken pre-vaccination (Day 0) and post-vaccination (Day 7), and

using the intracellular cytokine staining (ICS) assay on samples taken pre-vaccination (Day 0), post-vaccination (Day 7) and 1 month post-vaccination (Day 30).

Influenza-specific interferon-gamma (IFN-γ) production was assessed using the QuantiFERON®-CMI assay and ICS.

The number and percentage of responders were tabulated by Study Vaccine and cohort. Logistic regression models were used to assess the effect of increasing adjuvant dose on T cell response rates, incorporating covariate adjustments for age, sex, health status, pre-vaccination titres and previous influenza vaccination history. Specific linear contrasts were used to compare the immune responses in Cohort B (≥ 60 years) receiving adjuvanted vaccines to the immune responses in Cohort A (≥ 18 to ≤ 45 years) receiving unadjuvanted vaccine or lower doses of adjuvant, to assess the ability of adjuvant to restore immune responses of older adults (≥ 60 years) to levels seen in the younger cohort.

SUMMARY – CONCLUSIONS

IMMUNOGENICITY RESULTS:

Primary analysis (HI antibody results against CPMP criteria)

Cohort A (Adults)

In adults (≥18 to ≤45 yrs) the HI data for the H_1N_1 (New Caledonia/20/99-like) strain, the H_3N_2 (A/Wisconsin/67/2005-like) strain and the B/Malaysia/2506/2004-like strain met all serological criteria (seroconversion and/or significant increase, mean geometric fold increase and sero-protection) for all treatment groups.

Cohorts B, C, and D (Older Adults)

In the older adult study cohorts, CSL412 formulations (adjuvanted vaccine) performed at least as well or better compared with Enzira® Vaccine under CPMP criteria.

The HI data for the H_1N_1 (New Caledonia/20/99-like) strain, the H_3N_2 (A/Wisconsin/67/2005-like) strain and the B/Malaysia/2506/2004-like strain met at least one of the serological criteria (seroconversion and/or significant increase, mean geometric fold increase and sero-protection) for all treatment groups.

Overall, all CSL412 formulations (adjuvanted vaccines) performed at least as well or better against the CPMP criteria compared with Enzira® Vaccine.

Antibody Dose-Response

An antibody dose-response to ISCOMATRIX® adjuvant was observed for some vaccine influenza strains in covariate adjusted regression models. Antibody dose-response was evaluated through a series of unadjusted and covariate adjusted regression models with two major endpoints: 1) the proportion of participants with seroconversion/significant increase in HI titre; and 2) the log fold increase in HI titre.

For the log fold increase in HI titre regressions, the unadjusted analysis comparing Cohorts A and B indicated significantly higher antibody results against all three vaccine strains for Cohort A relative to Cohort B, but no significant adjuvant dose-response on HI antibody levels. However, for the covariate adjusted model there was a significant ISCOMATRIX® adjuvant dose-response for the B virus strain (as measured by the fold increase per µg ISCOMATRIX®) 1.003 [95% CI: 1.001, 1.005]. After adjusting for covariates, there were no longer statistically significant differences between Cohorts A and B HI antibody levels for any virus strain. This suggests that the covariates (age, sex, pre-vaccination HI titres and previous influenza vaccination history) accounted for the majority of differences observed between Cohort A and B in the unadjusted model.

A similar pattern of results was seen for the second HI endpoint assessed by regression models, the proportion of participants with seroconversion/significant increase in HI titre. For the

covariate adjusted model, there was a significant ISCOMATRIX® adjuvant dose-response for both the H_3N_2 and B virus strains (as measured by the Odds per µg ISCOMATRIX®). For the H_3N_2 strain, this result was 1.010 [95% CI: 1.003, 1.017], and for the B strain was 1.008 [95% CI: 1.002, 1.014]. Significant differences between Cohorts A and B in the unadjusted model were no longer statistically significant after covariate adjustment.

Cell-Mediated Immunogenicity Assessments

Th1-type IFN-γ response

Strong Th1-type IFN-γ responses to vaccination, as measured by the QuantiFERON®-CMI assay following influenza virus antigens stimulation, were detected in all cohorts with all CSL412 (adjuvanted vaccine) treatments, relative to the responses to Enzira® Vaccine.

For the Cohorts BCD combined analysis, the post-vaccination Th1-type IFN-γ geometric mean concentration (GMC) was much higher for the Influenza Vaccine + 120 µg ISCOMATRIX® adjuvant treatment group (26.98 [95% CI: 22.320, 32.611]; geometric fold increase: 4.64) compared with the Enzira® treatment group (8.50 [95% CI: 6.883, 10.508]; geometric fold increase: 1.57). These results correspond with a much higher responder rate for the Influenza Vaccine + 120 µg ISCOMATRIX® adjuvant treatment group (67.6%) compared with the Enzira® treatment group (22.2%).

For the Cohort B analysis, which also investigated the 30 µg and 60 µg ISCOMATRIX® adjuvant treatment groups, the Influenza Vaccine + 120 µg ISCOMATRIX® adjuvant treatment group had the highest post-vaccination Th1-type IFN-γ GMC (35.91 [95% CI: 25.938, 49.721]; geometric fold increase: 4.32), and associated highest responder rates (66.1%).

CTL IFN-γ response

CTL IFN-γ responses to vaccination, as measured by the QuantiFERON®-CMI assay following Influenza CTL Epitope stimulation, were low for all cohorts with all CSL412 and Enzira® Vaccine treatments. Therefore, a specific Cytotoxic Lymphocyte $CD8^+$ response (CTL) was not demonstrated by the QuantiFERON®-CMI assay.

CTL (CD8+) IFN-γ+ responses to vaccination, as measured by the Intracellular Cytokine Stimulation (ICS) assay following CTL Influenza Epitope stimulation or following influenza virus antigens stimulation showed either minimal responses to treatments, or considerable variability in the pattern of results between CSL412 and Enzira® Vaccine treatments.

Th2-type IL-10 response

Strong Th2-type IL-10 responses to vaccination, as measured by the EIA following influenza virus antigens stimulation, were detected in all cohorts with all CSL412 treatments. As for the Th1-type IFN-γ responses, the responses to vaccination were considerably greater for all CSL412 treatments, relative to the responses to Enzira® Vaccine.

Ratio of Th1-type IFN-γ:Th2-type IL-10 response

In general, vaccination with study treatments in most cohorts resulted in a decrease in the post-vaccination Th1-type IFN-γ:Th2-type IL-10 ratio relative to the pre-vaccination ratio. This indicates a relative shift post-vaccination to more of a Th2-type IL-10 cytokine response.

Cell-Mediated Immunogenicity (CMI) Dose-Response

A strong and significant CMI dose-response to ISCOMATRIX® adjuvant was observed for the Th1-type IFN-γ response and Th2-type IL-10 response measures in regression models. CMI dose-response was evaluated through a series of unadjusted and covariate adjusted regression models with four major endpoints: 1) the Th1-type IFN-γ response; 2) the CTL IFN-γ response; 3) the Th2-type IL-10 response; and 4) the ratio of Th1-type IFN-γ:Th2-type IL-10 response.

For the unadjusted regression of the Th1-type IFN-γ response, there was a significant adjuvant dose-response as measured by the fold increase in IFN-γ concentration per µg adjuvant, with a regression coefficient of 1.005 (95% CI: 1.003, 1.007, $p<0.001$). No significant cohort effect comparing Cohorts A and B was noted. For the covariate adjusted regression of the Th1-type IFN-γ response, there remained a significant adjuvant dose-response, 1.006 (95% CI: 1.004, 1.008, $p<0.001$).

Neither a cohort nor an adjuvant dose-response was seen in unadjusted or covariate adjusted

models for the CTL IFN-γ response.

For the unadjusted Th2-type IL-10 response regression, there was a significant adjuvant dose-response as measured by the fold increase in IL-10 concentration per µg adjuvant, with a regression coefficient of 1.006 (95% CI: 1.004, 1.008, p<0.001). There was also a highly significant cohort effect comparing Cohorts A and B, with a GMC ratio of 1.758, (95% CI: 1.334, 2.316, p<0.001). For the covariate adjusted regression of the Th2 type IL-10 response, there remained a significant adjuvant dose-response, 1.005 (95% CI: 1.004, 1.007, p<0.001) GMC per µg of adjuvant dose.

There was a highly significant cohort effect comparing Cohorts A and B for the unadjusted models for the ratio of Th1-type IFN-γ:Th2-type IL-10 response, but no significant adjuvant dose effect. There was neither a significant cohort nor an adjuvant dose-response seen in the covariate adjusted model for this endpoint.

SAFETY RESULTS:

CSL412 (adjuvanted vaccine) formulations and Enzira® (unadjuvanted vaccine) were both well tolerated by all study cohorts. With regards to the primary safety endpoint, only one Cohort A participant in the 30 µg adjuvanted group experienced Grade 3 fever of a single day duration. No other participants experienced fever (Grade 3 or 4), injection site ulceration, necrosis or abscess during the Active Study Period.

The incidence of SAEs was low, and all SAEs were considered either to be unrelated or unlikely to be related to the Study Vaccine. The majority of SAEs were experienced by participants in Cohort D (Older Adults ≥ 60 years in Long-Term Care Facilities) and the pattern of events reported was consistent with the co-morbidities of an elderly population.

Solicited injection site AEs were commonly reported by all Study Vaccine groups irrespective of the treatment allocation with mild grade pain being the most frequently reported event. Solicited injection site AEs were reported in a greater proportion of participants in the adjuvanted groups with a shift in intensity to moderate grade events noted. Few severe grade events of redness, swelling or induration were experienced and there was one severe grade event of pain in a Cohort A participant in the 120 µg adjuvanted group. Within the adjuvanted groups, particularly in Cohort BCD, similar proportions of participants reported injection site events in both the 30 µg and 60 µg groups with a slightly higher percentage reporting events in the 120 µg group as compared with the 30 µg group. Solicited injection site AEs were on average resolved within 3 days.

Solicited systemic AEs were reported by proportionally more participants receiving adjuvanted vaccine as compared with the unadjuvanted groups. Within the target population Cohort BCD, overlapping confidence intervals were evident when assessing events overall and each individual symptom. The majority of solicited systemic AEs reported were mild to moderate in intensity grade in all cohorts. No clear pattern of an adjuvant dose effect on the overall incidence of all systemic AEs or individual symptoms was evident.

The majority of unsolicited treatment emergent AEs were of mild to moderate grade intensity and most were not related to Study Vaccine. The spectrum of unsolicited AEs reported in the older adults reflected co-morbidities in this population.

In terms of laboratory results, no clinically significant difference was observed between cohorts or treatment groups.

In conclusion, the addition of ISCOMATRIX® adjuvant is associated with a higher incidence of solicited AEs, particularly injection site AEs. However the majority of events are mild to moderate grade severity, and notably pain was very infrequently reported as severe grade intensity. Thus the adjuvant does not appear associated with adverse overt reactogenicity. Importantly whilst the immune response, as evidenced by HI and GMC, is improved by the adjuvant in the target older adult population of Cohort BCD to approximate that of the unadjuvanted Cohort A adult group, the reactogenicity profile is not adversely compromised for this effect, since adverse event rates in the older adult Cohort BCD adjuvanted group remained lower than that reported for Enzira® in the Cohort A adult group. Therefore, in the context of CSL412 use in the older adult population, the observed reactogenicity in this study, when balanced against the potential benefit of enhanced immunogenicity and protection against complications of influenza infection, indicates a favourable risk benefit profile for CSL412.

CONCLUSION:

All three formulations of CSL412 (adjuvanted vaccine containing 30 µg, 60 µg or 120 µg ISCOMATRIX® adjuvant) and Enzira® Vaccine, met the *CPMP/BWP/214/96* immunogenicity criteria for the Study population.

Comparison between CSL412 formulations and Enzira® Vaccine in Older Adult Cohorts (target population for CSL412):

- For the Older Adult cohorts, CSL412 formulations consistently resulted in increased HI serological responses as measured by post-vaccination GMTs, and immunogenicity responses specified by the *CPMP/BWP/214/96* criteria. In exploratory cell-mediated immunity assessments for the Older Adult cohorts, CSL412 formulations consistently resulted in increased T cell responses to:
    - the Th1-type IFN-γ responses by the QuantiFERON®-CMI assay;
    - IL-10 responses by Enzyme Immunoassay; and
    - $CD4^{+}IFN\text{-}\gamma^{+}$ Th1-type responses to vaccination by the Intracellular Cytokine Staining (ICS) assay.
- Enzira® Vaccine (2006/2007) and all three formulations of CSL412 containing different doses of adjuvant, administered as a single dose (0.5 mL), appears safe and generally well tolerated, especially in the targeted population of the Older Adults (≥ 60 years).

Date of the Results Summary: 09-MAR-2016