



Food and Drug Administration  
Center for Biologics Evaluation and Research  
Office of Biostatistics and Epidemiology  
Division of Biostatistics

# STATISTICAL REVIEW AND EVALUATION BLA

**BLA/Supplement Number:** 125408/0

**Product Name:** Flucelvax® cell-culture derived seasonal influenza vaccine

**Indication(s):** Active immunization of persons aged 18 years and older against influenza disease caused by influenza virus subtypes A and type B present in the cell-culture derived vaccine

**Applicant:** Novartis Vaccines and Diagnostics, Inc.

**Date(s):** Date submitted: November 1, 2011  
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**Review Priority:** Standard

**Statistical Branch:** Vaccine Evaluation Branch

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## 1. EXECUTIVE SUMMARY

This submission includes a Biological License Application (BLA STN 125408/0) which contains data and summarization of efficacy, immunogenicity, and safety responses from seven (7) studies and one extension study for a total of eight (8) studies to determine the safety, tolerability, and immunogenicity of Novartis's novel Cell-Culture Derived Influenza Vaccine: Flucelvax® (name changed in Summer 2012 from Optaflu®) or CCI/cTIV (the acronyms used in applicant provided studies) in adult populations 18+ years old. These studies were performed in a variety of US and non-US sites with a few studies performed under US-IND, while the majority of studies were not performed under US-IND. It should be noted that the pivotal Phase III study performed under US-IND did meet the pre-specified criteria establishing the efficacy and immunogenicity of this product. At least two of the Phase III studies initially were designed only to provide descriptive statistics (which is the immunogenicity requirements of the European regulatory agency), and after the studies were completed the data were analyzed using retrospective hypothesis tests related to immunogenicity to serve as primary endpoints, based on US definition and criteria, for submission to the US FDA.

### *1.1 Conclusions and Recommendations*

Based on the efficacy and immunogenicity endpoints data and an acceptable safety profile provided within BLA 125408 amendment 0, it appears that the potential clinical benefits outweigh the known risks for this product. Specifically, the pivotal Phase III study performed under US-IND did meet the pre-specified criteria establishing the efficacy and immunogenicity of this product. Approximately 4,000 adult subjects were exposed to Flucelvax®/CCI within the US under US-IND.

### *1.2 Brief Overview of Clinical Studies*

The submission in BLA 125408 amendment 0 included study results of 7 studies from Phase I to Phase III in adult subjects 18 years of age and older as well as one additional pediatric study. The components of this BLA contained within this submission included:

- Module 1 Volume 1: Administrative Information, Labeling
- Module 2 Volume 1: Clinical Summary of Safety and Efficacy
- Module 5 Volumes 1-5: Complete Study Reports for the seven (7) studies
  - V58P1 (Germany)
  - V58P2 (New Zealand)
  - V58P4 (Poland)
  - V58P4E1 (Poland)
  - V58P5 (US)
  - V58P9 (Lithuania)
  - V58P13 (US, Finland, Poland)
  - V58P12 (US, Finland, Lithuania, Hungary, Romania, Italy, Croatia)

Case Report Forms, SAE Report Forms, Post-Marketing Reports, and literature.

This review will focus on the primary Phase III studies including:

- V58P13
- V58P4
- V58P9

A detailed summary of the studies, including study number (as per the applicant: Novartis), geographic location, objective of the study, study design, and control, Flucelvax®/CCI product including dosage regimen and route of administration, subjects exposed, age studied, and study status/duration, is included in the table below. Efficacy was assessed in the pivotal study V58P13. Safety and immunogenicity were assessed in all seven studies. The study populations for V58P1, V58P2, V58P4, and V58P4E1 were originally stratified into 18 to 60 years and  $\geq 61$  years of age at enrollment, since these studies were designed to support a European marketing authorization application, while studies V58P9 and the US study V58P5 were conducted only in adults aged 18 to 60 and 18 to 49 years, respectively. Immunogenicity and safety results of studies V58P1, V58P2, V58P4, and V58P4E1 were retrospectively re-analyzed stratifying study populations into age groups 18 to 64 years and  $\geq 65$  years of age.

**Table 1** Summary of Phase I, II and III Studies to examine the safety, immunogenicity and/or tolerability of Flucelvax®/CCI

| Study Number           | Geographic Location  | Objective(s) of the Study                    | Study Design and Type of Control                              | Test Product(s); Dosage Regimen; Route of Administration          | Subjects Exposed              | Age  | Study Duration |
|------------------------|--|--|---|---|-------------------------------|--|----------------|
| V58P1                  | Germany  | Safety<br>CHMP criteria                      | Phase I/II, observer blind, randomized, controlled            | cTIV;<br>eTIV-a, formulation<br>2001-2002 <sup>a</sup> *          | Phase 1: 40;<br>Phase II: 200 | Phase 1:<br>18-40<br>Phase II:<br>18-64 and<br>≥65 yrs | 3 weeks        |
| V58P2                  | New Zealand  | CHMP criteria                                | Phase II, observer blind, randomized, controlled              | cTIV;<br>eTIV-a, formulation<br>2003 <sup>b</sup>                 | 223                           | 18-64 and<br>≥65 yrs                                   | 3 weeks        |
| V58P4                  | Poland   | Non-inferiority<br>of cTIV vs.<br>eTIV-a     | Phase III, observer blind, randomized, controlled             | cTIV;<br>eTIV-a, formulation<br>2004-2005 <sup>a</sup>            | 2654                          | 18-64 and<br>≥65 yrs                                   | 6 months       |
| V58P4E1                | Poland   | “Cross-over”<br>revaccination at<br>one year | Phase III, observer blind, randomized, controlled             | cTIV;<br>eTIV-a, formulation<br>2005-2006 <sup>a</sup>            | 2235                          | 18-64 and<br>≥65 yrs                                   | 6 months       |
| V58P5                  | US   | Non inferiority<br>of cTIV vs<br>eTIV-f      | Phase II, observer blind, randomized, controlled              | cTIV;<br>eTIV-f, formulation<br>2005-2006 <sup>a</sup>            | 613                           | 18-49 yrs  | 6 months       |
| V58P9                  | Lithuania  | Lot comparison<br>of cTIV                    | Phase III, observer blind, randomized, controlled, lot-to-lot | cTIV;<br>eTIV-a, formulation<br>2005-2006 <sup>a</sup>            | 1200                          | 18-60 yrs  | 6 months       |
| V58P13                 | US, Finland, Poland  | Efficacy of<br>cTIV<br>and eTIV-a            | Phase III, observer blind, randomized, placebo controlled     | cTIV;<br>cTIV-a; formulation 2007-<br>2008 <sup>a</sup> ; placebo | 11,376                        | 18-49 yrs  | 6 months       |
| V58P12<br>(supportive) | US, Finland, Lithuania,<br>Hungary, Romania,<br>Italy, Croatia | Non-inferiority<br>of cTIV vs.<br>cTIV-f     | Phase II/III, observer blind, randomized, controlled          | cTIV;<br>cTIV-f;<br>formulation 2007-2008 <sup>a</sup>            | 3604                          | 3-8 yrs<br>9-17 yrs                                    | 6 months       |

<sup>a</sup> Northern hemisphere; <sup>b</sup> Southern hemisphere.

\* Phase 1 and 2 study V58P1 was conducted during influenza season 2002/2003 but used the recommended influenza vaccine composition from the preceding season.

cTIV: Cell Culture-derived Influenza Vaccine eTIV-a: Egg-derived Influenza vaccine, Agriflu eTIV-f: Egg-derived Influenza vaccine, Fluvirin

**V58P1-**Study V58P1 was a sequential, Phase I and Phase II study conducted in a stepwise fashion in 2002. The first part (Phase I) was conducted in 40 healthy subjects, 18 to 40 years of age. Subjects were enrolled and observed for at least 1 week with telephone calls on days 3 and 7 to check their health status. After the investigators established that the study vaccines were well tolerated, 200 additional subjects 18 to 60 years and  $\geq 61$  years of age were enrolled in the second part (Phase II) of the study.

**V58P2-**Study V58P2 was a Phase II study carried out 6 months later (2003) in the southern hemisphere in 223 healthy adult subjects  $\geq 18$  years of age.

The sample sizes of these studies (V58P1 and V58P2) were expected to be adequate to evaluate potential safety signals for commonly occurring AEs within the 3-week follow-up.

**V58P3-**Upon completion of study V58P2, including observation of acceptable immunogenicity and safety results, a Phase III study, V58P4, was performed in 2004. A total of 2654 healthy adults  $\geq 18$  years of age were enrolled and followed for 6 months. The study was powered to demonstrate non-inferiority of the cTIV compared with eTIV-a as control vaccine as secondary objective. A year later, the same subjects were asked to participate in an extension study V58P4E1. Of the subjects who were enrolled into V58P4, 2235 (84%) consented to participate in the extension study. Subjects who had received cTIV in the previous year were randomized at a 1:1 ratio to receive either the cTIV or the control vaccine. Subjects previously administered the control were similarly randomized. Considering the vaccine received the previous influenza season (V58P4), there were a total of four treatment groups (cTIV/cTIV, cTIV/control, control/cTIV, and control/control). As per the applicant, the design of this extension study was specifically intended to mirror the “real life” situation of future influenza vaccination campaigns in which subjects may receive a vaccine from a different source (egg or cell culture) in different years. Potential safety issues related to repeated exposure to the cTIV during a one-year interval and the possible persistence of antibody titers after one year were also to be collected and examined within this study.

**V58P9-**A large, active-controlled Phase III study, V58P9, not under US-IND, was conducted in 1200 subjects during the influenza season 2005/2006. This study investigated whether immunogenicity and safety results were consistent for three production lots of cTIV in subjects aged 18 to 60 years in a post hoc manner. In addition, immunogenicity and safety were analyzed 6 months after vaccination.

**V58P5-**In the same influenza season, a Phase II study (V58P5) was conducted in the US and demonstrated non-inferiority of the cTIV compared with eTIV-f (Fluvirin) as control vaccine. This study included 613 subjects (309 exposed to cTIV, 304 to control).

**V58P12-**In 2007/2008 study V58P12 was conducted in Finland, Croatia, the US, Italy, Lithuania, Romania, and Hungary. This study examined the safety and efficacy of cTIV in healthy children and adolescents aged 3 to 17 Years. This study enrolled a total of 3604 subjects (2264 exposed to cTIV, 1340 to control).

**V58P13-**A large pivotal, placebo controlled Phase III efficacy study (V58P13) enrolled 11404 subjects (11382 subjects received a vaccination: cTIV 3814 subjects, eTIV-a (Agriflu) 3671

subjects and placebo 3897 subjects) to investigate vaccine efficacy of cTIV compared with placebo and eTIV-a compared with placebo for the prevention of virus-confirmed symptomatic influenza A or B illness, defined as influenza wild type strains antigenically matched to those contained in the vaccines. Safety was assessed in all exposed subjects who provided post vaccination safety data and immunogenicity was investigated in a subset of subjects.

With a total safety population of 6138 cTIV subjects, since no SAE related to vaccine administration was reported in the pooled exposed safety database of the cTIV vaccine, it can be inferred that with 95% confidence the true vaccine-related serious adverse event rate is  $<0.0005$  ( $<1$  in 2000).

Overall, the data provided in the Original BLA submission, BLA 125408 amendment 0, suggests that Flucelvax®/CCI is safe and efficacious (based on immune response in the majority of studies and efficacy in one study) in adults 18 + years of age.

### ***1.3 Major Statistical Issues and Findings***

This BLA provided the results of 8 studies including Phase I, Phase II and Phase III studies that examined the administration of Flucelvax®/CCI to adult and pediatric subjects under US-IND and non-US-IND studies performed in US and non-US sites.

Several studies in this submission were under US-IND and were well-controlled (V58P5 and V58P13). However, many supportive studies provided in this submission (Phase I, Phase II, and Phase III) were not performed under US-IND or included analysis on immunogenicity endpoints that were based on post-hoc statistical hypotheses. This may be acceptable, considering the criteria for immunogenicity endpoints utilized by the applicant are clearly defined in the FDA Guidance for licensing Seasonal Influenza Vaccines. The lot-to-lot consistency study (V58P9) had issues related to study planning and data limitations. The issues included: 1) the study was defined as a lot consistency study post-hoc, and 2) one of the two sites (with ~40% of the subjects) was excluded from the analysis because of data integrity issues.

The immune response data for both seroprotection and seroconversion show sufficient response to meet the criteria based on the FDA Guidance for licensing Seasonal Influenza Vaccines (for adults; there is no pediatric guidance as of Sept. 2012) for all strains in the pivotal study. Additionally, the pivotal Phase III study performed under US-IND, study V58P13, met the pre-specified criteria related to the prevention of matched strain influenza illness, establishing the efficacy of this product. Finally, the adverse events reported within this study are consistent with other flu products. The most commonly occurring adverse events included injection site pain and erythema, which were resolved quickly (within 1-7 days).

## ***2. INTRODUCTION***

### ***2.1 Overview***

On November 1, 2011 Novartis submitted a Biological License Application (BLA) for a cell-culture derived trivalent seasonal influenza vaccine with the proposed trade name

Flucelvax®/CCI seeking approval for administration in Adults 18 year of age or older in the prevention of seasonal influenza. This submission includes the results of eight Phase I-III studies that examined the immunogenicity, efficacy, and safety/tolerability of this influenza vaccine product under US and non-US IND. The results of select studies will be examined in detail within this review.

## ***2.2 Data Sources***

Data sources include the paper copy of Novartis's provided study reports and data sets. The datasets including subject immune responses, AEs, demographics, etc., were located within the CBER EDR:

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## **3. *STATISTICAL EVALUATION***

This submission contains a BLA in support of licensure for the administration of Flucelvax®/CCI, a seasonal influenza cell-culture vaccine to be administered in adult populations. Included in the submission are the results of eight Phase I, Phase II, and Phase III studies:

V58P1 (Germany)  
V58P2 (New Zealand)  
V58P4 (Poland)  
V58P4E1 (Poland)  
V58P5 (US)  
V58P9 (Lithuania)  
V58P13 (US, Finland, Poland)  
V58P12 (US, Finland, Lithuania, Hungary, Romania, Italy, Croatia)

as well as Case Report Forms, SAE Report Forms, Post-Marketing Reports, and literature references.

This statistical review will focus on the primary Phase III studies including:

- V58P13
- V58P4
- V58P9

### ***3.1 Evaluation of Efficacy and Safety- Study V58P13***

#### **3.1.1. Design Overview**

Study V58P13 was, as per the applicant, “A Phase III, Randomized, Observer-Blind, Placebo-Controlled, Multicenter/Multinational Study to Assess Clinical Efficacy of a Cell-Derived Subunit Influenza Vaccine and an Egg-Derived Subunit Influenza Vaccine administered in Healthy Adult Subjects between Sept 2005 and April 2006.” This study involved seventeen sites in the US, eleven in Finland, and twenty-four in Poland.

### **Primary Objectives for Efficacy**

To demonstrate protection of a cell culture-derived influenza (CCI) vaccine compared with placebo and protection of an egg-derived influenza vaccine (IVV) compared with placebo against illness caused by virus-confirmed community-acquired influenza wild type strains antigenically similar to those contained in the vaccine.

### **Secondary Objectives**

#### **Efficacy:**

To evaluate if the cell culture-derived and the egg-derived vaccines, when compared with placebo:

- protect against illness caused by all virus-confirmed community-acquired influenza wild type strains a) regardless of antigenic match and b) dissimilar to those contained in the vaccines;
- reduce the number of days in bed associated with cases of virus-confirmed influenza;
- reduce the number of inpatient and outpatient medical visits due to influenza illness or symptoms of influenza;
- reduce the number of days of usual activity (i.e., job, school, household/ family/ community activities) lost due to influenza disease.

#### **Immunogenicity:**

To evaluate immunogenicity (in a subset of subjects) measured by the percentage of subjects achieving seroprotection and seroconversion 21 days after vaccination.

#### **Safety:**

To evaluate safety and tolerability of a cell culture-derived influenza vaccine and an egg-derived vaccine, each compared with placebo.

### **Methodology**

This Phase III, randomized, observer-blind, placebo-controlled, multi-center study was performed over a period of approximately 9 months at multiple study sites in the US, Poland, and Finland. The study included both a CCI vaccine arm and an IVV arm. The efficacy of each of the two influenza vaccines was compared separately against a single placebo arm, thus minimizing the number of subjects who received placebo. Subjects aged 18 to 49 years were

randomly allocated at a 1:1:1 ratio to receive CCI vaccine, IVV, or placebo, and were followed for approximately 28 weeks after vaccination. The first 1045 subjects enrolled and randomized at the US sites were included in an immunogenicity subset according to an unbalanced randomization ratio of 8:25:2 to receive CCI vaccine, IVV, or placebo, respectively, based on the sponsor’s interest in this study to examine the immunogenicity effect of the egg-derived product: Agriflu®.

**Number of Subjects (planned and analyzed)**

Approximately 11,700 subjects were planned to be enrolled in this study (3900 subjects per each of the three vaccine/placebo groups); 11404 subjects were actually enrolled. The number of subjects planned and actually analyzed in the immunogenicity subset and the number of subjects planned in the entire study are presented in the table below:

**Table 2** Summary of subjects enrolled

| Overall Number of Subjects (Planned) Actual |                      |             |             | Immunogenicity Analysis (Planned) Actual |             |         |
|---|----------------------|-------------|-------------|--|-------------|---------|
| Total Cohort Europe                         | Total (7800) 6397    |             |             | Total Not Planned                        |             |         |
|   | Cell culture-derived | Egg-derived | Placebo     | Cell culture-derived                     | Egg-derived | Placebo |
|   | (2600) 2128          | (2600) 2135 | (2600) 2134 | (-)                                      | (-)         | (-)     |
| Total Cohort US                             | Total (3900) 5007    |             |             | Total (1050) 1045                        |             |         |
|   | Cell culture-derived | Egg-derived | Placebo     | Cell culture-derived                     | Egg-derived | Placebo |
|   | (1300) 1700          | (1300) 1541 | (1300) 1766 | (240) 240                                | (750) 746   | (60) 59 |
| Overall Total                               | Cell culture-derived | Egg-derived | Placebo     | Cell culture-derived                     | Egg-derived | Placebo |
| (11,700) 11,404                             | (3900) 3828          | (3900) 3676 | (3900) 3900 | (240) 240                                | (750) 746   | (60) 59 |

**Diagnosis and Main Criteria for Inclusion and Exclusion**

Subjects eligible for enrollment into this study were healthy male and female adults 18 to 49 years of age, in good health as determined by medical history and physical examination, able and willing to give written informed consent prior to study entry; able to comply with all the study procedures, including availability and willingness to be actively followed throughout the

ensuing influenza season with weekly telephone calls and to comply with the need for prompt collection of nasal and throat specimens in the event of influenza-like illness (ILI).

## **Duration of Study**

The duration of the enrollment was approximately 8 weeks. Each study subject was observed for 6 months after vaccination or for the whole surveillance period, whichever was longer. The total duration of the study was approximately 9 months.

## **Criteria for Evaluation**

### Efficacy

The primary study endpoint was the estimate of vaccine efficacy (VE) of cell culture-derived influenza vaccine compared with placebo and egg-derived influenza vaccine compared with placebo for the prevention of virus-confirmed symptomatic influenza A or B illness, defined as influenza wild type strains antigenically similar to those contained in the vaccines. Each vaccine was to be considered statistically compliant with the May 2007 CBER Guidance for Industry criteria for estimating VE against placebo if the lower limit of the one-sided simultaneous 97.5% Confidence Interval (CI) for the estimate of VE relative to placebo was greater than 40%.

Secondary measures of efficacy included estimates and associated one-sided 97.5% simultaneous CIs for the VE of cell culture-derived influenza vaccine compared with placebo and egg-derived influenza vaccine compared with placebo for the prevention of virus-confirmed symptomatic influenza A or B illness, defined as influenza wild type strains regardless of antigenic match to those contained in the vaccine and dissimilar to those contained in the vaccine.

Additionally, the mean number of days in bed associated with cases of virus-confirmed influenza, the mean number of inpatient and outpatient medical visits due to influenza illness or symptoms of influenza, and the mean number of days of usual activity lost due to influenza disease were summarized and compared between the cell culture-derived influenza vaccine and placebo and between the egg-derived influenza vaccine and placebo.

### Immunogenicity

For the immunogenicity subset, the percentage of subjects seroprotected or achieving seroconversion were to be considered statistically compliant with the stated May 2007 CBER Guidance for Industry criteria if for all three strains:

- the lower limit of the two-sided 95% CI for the percentage of subjects achieving an HI antibody titer  $\geq 40$  met or exceeded 70%;
- the lower limit of the two-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody met or exceeded 40%.

### Safety

- The safety of the study vaccines was assessed in terms of numbers and percentages of subjects exposed to study vaccines with reported solicited and unsolicited AEs.

**Statistical Methods:** The null hypotheses for the primary objectives state that the influenza vaccines do not comply with the assumption that the lower limits of the one-sided 97.5% CIs are >40%. Assuming a VE of 70% (where  $VE = 1 - \text{relative risk}$ ) for both the cell culture-derived and egg-derived influenza vaccines and an influenza virus attack rate of 3%, the sample size of 3500 evaluable subjects per vaccine group had 92% power to ensure that each of the lower limits of the one-sided 97.5% CIs for VE was greater than 40% (Poisson approximation). The efficacy of the two vaccines relative to placebo against wild type strains antigenically similar to the vaccine strains was assessed using simultaneous  $100(1-\alpha)\%$  Sidak-corrected one-sided score confidence intervals for the two relative risks, where  $\alpha=0.025$ . The two simultaneous confidence intervals were constructed by inverting the score test for the following hypotheses comparing each influenza vaccine to placebo.

$H_{0\text{ CCI}}$ : VE cell culture-derived vaccine  $\leq 40\%$        $H_{0\text{ IVV}}$ : VE egg-derived vaccine  $\leq 40\%$   
 vs  
 $H_{1\text{ CCI}}$ : VE cell culture-derived vaccine  $> 40\%$        $H_{1\text{ IVV}}$ : VE egg-derived vaccine  $> 40\%$

Or equivalently in terms of relative risk (RR):

$H_{0\text{ CCI}}$ : RR cell culture-derived vaccine  $\geq 0.60$        $H_{0\text{ IVV}}$ : RR egg-derived vaccine  $\geq 0.60$   
 vs  
 $H_{1\text{ CCI}}$ : RR cell culture-derived vaccine  $< 0.60$        $H_{1\text{ IVV}}$ : RR egg-derived vaccine  $< 0.60$

The placebo group was used as the control to estimate the two VEs individually (i.e., VE of the cell culture-derived vaccine, VE of the egg-derived vaccine).

This study was powered to demonstrate that the VE of each vaccine compared with placebo was different from 40% and not to compare the two influenza vaccine groups in terms of vaccine efficacy. However, with respect to immunogenicity, with 240 evaluable subjects in the cell culture-derived vaccine group, the lower limits of the two-sided 95% CIs around the estimated percentage of subjects seroprotected or achieving seroconversion for HI antibody at day 22 would meet or exceed the threshold levels of 70% and 40%, respectively, if seroprotection was at least 76% (95% CI, 70% to 83%) and the percentage of subjects with seroconversion in HI titer was at least 46.5% (95% CI, 40% to 54%). Secondary immunogenicity objectives and safety objectives were evaluated descriptively.

**Definition of Analysis Populations** (note: this was consistent and applies to all studies examined and discussed in this review)

Modified Intention-to-treat (MITT) population, Immunogenicity

All randomized subjects who:

- 1) received the dose of vaccine
- 2) provided one evaluable serum sample before and one after baseline

Per-protocol (PP) population, Immunogenicity

All subjects in the MITT population who:

- 1) received the vaccination correctly
- 2) provided evaluable data before and after vaccination
- 3) experienced no major protocol violations, as defined before unblinding.

Safety

All subjects with vaccination and with some post-baseline safety data.

### **3.1.2. Results: Vaccine Efficacy and Immunogenicity**

Since there are no comparisons planned/made between CCI and IVV in this study and the CCI results are of primary interest for this licensure application, the IVV results will be included in the tables but the discussion will focus on the CCI results.

#### **Vaccine Efficacy against Vaccine-like strains**

A summary of the vaccine efficacy against the vaccine-like strains can be seen in the following table:

**Table 3 Vaccine Efficacy Against Culture-Confirmed Influenza Caused by Vaccine-like Strains – Per Protocol Population**

|         | Proportion of Subjects with influenza<br>(# Subjects/N) |                     |                     | Vaccine Efficacy<br>(VE%) <sup>1</sup> |                      | Simultaneous one-<br>sided 97.5% CI of<br>VE <sup>1</sup> |                      | P-Value <sup>2</sup> |                      |
|---------|---|---------------------|---------------------|--|----------------------|---|----------------------|----------------------|----------------------|
|         | CCI<br>(N=3776)   | IVV<br>(N=3638)     | Placebo<br>(N=3843) | CCI<br>vs<br>Placebo                   | IVV<br>vs<br>Placebo | CCI<br>vs<br>Placebo                                      | IVV<br>vs<br>Placebo | CCI<br>vs<br>Placebo | IVV<br>vs<br>Placebo |
| Overall | 0.0019<br>(7/3776)                                      | 0.00825<br>(9/3638) | 0.0114<br>(44/3843) | 83.8                                   | 78.4                 | 61.0  | 52.1                 | 0.0005 <sup>1</sup>  | 0.0035 <sup>1</sup>  |
| A/H3N2  | 0.005<br>(2/3776)                                       | 0.0005<br>(1/3638)  | 0<br>(0/3843)       | NE                                     | NE                   | NE  | NE                   | 0.9989               | 0.9915               |
| A/H1N1  | 0.0013<br>(5/3776)                                      | 0.0022<br>(8/3638)  | 0.0112<br>(43/3843) | 88.2                                   | 80.3                 | 67.4  | 54.7                 | 0.0001 <sup>1</sup>  | 0.0022 <sup>1</sup>  |
| B       | 0<br>(0/3776)   | 0 (0/3638)          | 0.0003<br>(1/3843)  | 100.0                                  | 100.0                | -410  | -429                 | 0.3936               | 0.4002               |

<sup>1</sup>Simultaneous one-sided 97.5% confidence intervals for the vaccine efficacy (VE) of each influenza vaccine relative to placebo based on the Sidak-corrected score confidence intervals for the two relative risks.

<sup>2</sup>Adjusted p-values are from the score statistic with Sidak correction testing the null hypothesis that the vaccine efficacy of each influenza vaccine relative to placebo  $\leq 40\%$  against the alternative hypothesis that the VE  $> 40\%$  (or equivalently, the null hypothesis that the relative risk (RR)  $\geq 0.60$  vs. the alternative hypothesis that RR  $< 0.60$ ). If the adjusted p-value is  $< 0.025$ , then the comparison is statistically significant.

VE = Vaccine Efficacy =  $(1 - \text{Relative Risk}) \times 100\%$

\*p<.025

From the above table, it can be observed that the cell culture derived influenza (CCI) vaccine protects against vaccine-like strains of influenza.

### Cell Culture-derived Influenza Virus (CCI) Vaccine

The rates of culture-confirmed influenza caused by vaccine-like strains in the per protocol efficacy population were 0.0019 (7/3776) in the CCI group and 0.0114 (44/3843) in the placebo group (VE = 83.8%). The lower limit (LL) of the simultaneous one-sided 97.5% CI for the VE of the CCI vaccine vs. placebo was 61% (p=0.0005).

Thus the CCI vaccine was considered to be statistically compliant with the May 2007 CBER guidance for industry criteria for estimating VE against placebo for preventing virus-confirmed symptomatic influenza A or B illness caused by vaccine-like strains, and the primary efficacy objective was met.

Particularly noteworthy were the results for the A/H1N1 strain, with an adjusted p-value of 0.0001 for the comparison of the VE to the CBER criterion. The associated VE and lower limit (LL) of the simultaneous one-sided 97.5% CI were 88.2% and 67.4%, respectively. For strain B, the VE was 100% as no influenza cases were reported in the CCI vaccine group, while one case was reported in the placebo group. Additionally, for the A/H3N2 strain, the VE of the CCI vaccine vs. placebo was not evaluable since no influenza case was observed in the placebo group.

Similar results were observed for the CCI vaccine group in the MITT population.

## **Secondary Efficacy Objectives**

### **VE against Non-vaccine-like strains**

A summary of the vaccine efficacy against the non-vaccine-like strains can be seen in the following table:

**Table 4** Vaccine Efficacy Against Culture-Confirmed Influenza Caused by Non-Vaccine-like Strains – Per Protocol Population

|         | Proportion of Subjects with influenza<br>(# Subjects/N) |                     |                     | Vaccine Efficacy<br>(VE%) <sup>1</sup> |                      | Simultaneous one-<br>sided 97.5% CI of<br>VE <sup>1</sup> |                      | P-Value <sup>2</sup> |                      |
|---------|---|---------------------|---------------------|--|----------------------|---|----------------------|----------------------|----------------------|
|         | CCI<br>(N=3776)   | IVV<br>(N=3638)     | Placebo<br>(N=3843) | CCI<br>vs<br>Placebo                   | IVV<br>vs<br>Placebo | CCI<br>vs<br>Placebo                                      | IVV<br>vs<br>Placebo | CCI<br>vs<br>Placebo | IVV<br>vs<br>Placebo |
| Overall | 0.0079<br>(30/3776)                                     | 0.0080<br>(29/3638) | 0.0193<br>(74/3843) | 58.7                                   | 58.6                 | 33.5  | 32.9                 | 0.0784               | 0.0846               |
| A/H3N2  | 0<br>(0/3776)   | 0.0005<br>(2/3638)  | 0.0021<br>(8/3843)  | 100.0                                  | 73.6                 | 36.3  | -30.0                | 0.0296               | 0.2651               |
| A/H1N1  | 0.0003<br>(1/3776)                                      | 0<br>(0/3638)       | 0.0021<br>(8/3843)  | 87.3                                   | 100.0                | 4.6   | 33.9                 | 0.1037               | 0.0327               |
| B       | 0.0077<br>(29/3776)                                     | 0.0074<br>(27/3638) | 0.0154<br>(59/3843) | 50.0                                   | 51.7                 | 17.5  | 19.4                 | 0.3756               | 0.3185               |

<sup>1</sup>Simultaneous one-sided 97.5% confidence intervals for the vaccine efficacy (VE) of each influenza vaccine relative to placebo based on the Sidak-corrected score confidence intervals for the two relative risks.

<sup>2</sup>Adjusted p-values are from the score statistic with Sidak correction testing the null hypothesis that the vaccine efficacy of each influenza vaccine relative to placebo  $\leq 40\%$  against the alternative hypothesis that the VE  $> 40\%$  (or equivalently, the null hypothesis that the relative risk (RR)  $\geq 0.60$  vs. the alternative hypothesis that RR  $< 0.60$ ). If the adjusted p-value is  $< .025$ , then the comparison is statistically significant.

VE = Vaccine Efficacy = (1 - Relative Risk) x 100 %

**CCI Vaccine:** The rates of culture-confirmed influenza caused by non-vaccine-like strains in the per protocol efficacy population were 0.0079 (30/3776) in the CCI group and 0.0193 (74/3843) in the placebo group (VE = 58.7%). The lower limit of the simultaneous one-sided 97.5% CI for the VE of the CCI vaccine vs. placebo was 33.5% (p=0.078). Thus, the CCI vaccine was not considered statistically compliant with the May 2007 CBER guidance for industry criteria for estimating VE against placebo for preventing virus-confirmed symptomatic influenza A or B illness caused by non-vaccine-like strains, and the secondary efficacy objective was not met. Similar results were observed for the CCI vaccine group in the MITT population.

### **VE against All (Vaccine-like and Non-vaccine-like) Circulating strains**

**CCI Vaccine:** The rates of culture-confirmed influenza caused by vaccine-like and non-vaccine-like strains in the per protocol efficacy population were 0.0111 (42/3776) in the CCI group and 0.0364 (140/3843) in the placebo group (VE = 69.5%). The lower limit of the simultaneous one-sided 97.5% CI for the VE of the CCI vaccine vs. placebo was 55.0% (p=0.000077). Thus, the CCI vaccine was considered to be statistically compliant with the May 2007 CBER guidance of industry criteria for estimating VE against placebo for preventing virus-confirmed symptomatic influenza A or B illness caused by vaccine-like and non-vaccine-like strains. Thus, the secondary efficacy objective was met.

Particularly noteworthy were the results for the A/H1N1 strain, with an adjusted p-value of 0.000006 for the comparison of the VE to 40%. The associated VE and LL of the simultaneous one-sided 97.5% CI were 89.3% and 73.0%, respectively. The observed VE was 75.6% for the A/H3N2 strain and 49.9% for the B strain.

Similar results were observed for the CCI Vaccine group in the MITT population.

Among the subset of subjects in the per protocol efficacy population who had culture-confirmed influenza and non-missing ILI follow-up data, there was no significant difference between the influenza vaccine groups and placebo in the mean number of days in bed, mean number of inpatient/outpatient visits due to influenza illness, or the mean number of days of usual activity lost due to influenza. However, expanding the number of subjects in the analysis to include all subjects in the per protocol efficacy population, there was a statistically significant difference between CCI and placebo (CCI mean = 0.04 days, n = 3775; placebo mean = 0.12 days, n = 3837, p < 0.0001) in the mean number of days in bed due to culture-confirmed influenza. Similar highly statistically significant results were also seen for the differences between each influenza vaccine group and placebo in the mean number of days of usual activity lost due to influenza, in the mean number of medical visits due to influenza, and in the mean number of outpatient visits due to influenza for all subjects in the per protocol efficacy population. These significant results largely reflect the difference among the vaccine groups in the rate of culture-confirmed influenza, since subjects in the per protocol population who did not have culture-confirmed influenza were analyzed as having spent 0 days in bed due to culture-confirmed influenza.

### **Immunogenicity**

#### ***Seroprotection***

At baseline, the percentages of seroprotected subjects were similar among the CCI vaccine group, IVV group, and the placebo group for all three strains. At day 22 post vaccination, the percentages of subjects achieving seroprotection increased in both vaccine groups and, as expected, did not increase in the placebo group (A/H1N1: 99% and 98% in the CCI vaccine and the IVV, respectively, vs. 60% in the placebo group; A/H3N2: 99% in both vaccine groups vs. 65% in the placebo group; B strain 78% and 92% in the CCI vaccine and IVV, respectively, vs. 22% in the placebo group).

#### ***Seroconversion***

At day 22 post vaccination the percentage of subjects achieving seroconversion was higher for all the strains in the CCI vaccine group compared with the placebo group where no seroconversion was expected [A/H1N1 strain (78%), A/H3N2 strain (59%) and B strain (51%) in the CCI vaccine].

The CBER criteria for seroprotection (the lower limit of the two-sided 95% CI for the percentage of seroprotected subjects at day 22  $\geq 70\%$ ) and for seroconversion (the lower limit of the two-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody titer at day 22  $\geq 40\%$ ) were met for all three influenza strains in the CCI vaccine group and not in the placebo group.

### 3.1.3. Results: Safety

Of the total 11404 subjects enrolled, 11376 subjects were included in the safety analysis set (3813, CCI vaccine, 3669, IVV and 3894, placebo). Of these individuals, a summary of subjects reporting any Adverse Events is as follows:

**Table 5** Overview of Adverse Events Days 1-7

|                             | Number(%) of Subjects with Adverse Events |               |                   |
|-----------------------------|---|---------------|-------------------|
|                             | CCI<br>N=3813                             | IVV<br>N=3669 | Placebo<br>N=3894 |
| Any AE                      | 350 (9%)                                  | 357 (10%)     | 371 (10%)         |
| Possibly related AE         | 212 (6%)                                  | 211 (6%)      | 206 (5%)          |
| Serious AE                  | 1 (<1%)                                   | 2 (<1%)       | 2 (<1%)           |
| AE leads to discontinuation | 0   | 0             | 0                 |
| Possibly related Serious AE | 0   | 0             | 0                 |
| Death                       | 0   | 0             | 0                 |

Overall, the percentages of subjects reporting any, local, and systemic solicited reactions were higher in the CCI vaccine group compared with the placebo group and in the IVV group compared with the placebo group. Across the three vaccine groups, the percentage of subjects experiencing local solicited reactions was higher than for systemic solicited reactions. The percentages of subjects experiencing other solicited reactions (i.e., the percentage of subjects staying at home and taking analgesic/antipyretic medications) were similar across all three vaccine groups.

A summary of the solicited reactions can be seen in the following table:

**Table 6** Overview of Solicited Reactions

|          | Number(%) of Subjects with Solicited Reactions |                   |                   |
|----------|--|-------------------|-------------------|
|          | CCI<br>N=381<br>3                              | IVV<br>N=366<br>9 | Placebo<br>N=3894 |
| Any      | 2016 (53%)                                     | 1780 (49%)        | 1500 (39%)        |
| Local    | 1527 (40%)                                     | 1283 (35%)        | 812 (21%)         |
| Systemic | 1134 (30%)                                     | 1044 (28%)        | 990 (25%)         |
| Other    | 409 (11%)                                      | 422 (12%)         | 400 (10%)         |

The most commonly reported local reaction in all three groups was pain followed by erythema. Pain was reported by a greater percentage of subjects in the CCI vaccine group compared with placebo (30% vs. 10%) and in the IVV group compared with placebo (24% vs. 10%). Most solicited local reactions were mild or moderate. Severe reactions were reported in <1% of subjects. Less than 1% of the subjects still reported solicited reactions after day 7.

The most common systemic reactions reported within 7 days of vaccination were headache, fatigue, myalgia, and malaise, each occurring in similar percentages of subjects across all three vaccine groups. No more than 1% of the subjects reported severe systemic reactions (arthralgia, sweating, chills), since most reactions in each of the three vaccine groups were of mild to moderate severity. Less than <1% of the subjects still reported solicited reactions after day 7.

The percentages of subjects with nonsolicited AEs, regardless of their assessment of relatedness, were balanced between the three groups: 9% to 10% of subjects reported AEs for days 1 to 7 when all AEs were collected; 3% of subjects in all three groups reported AEs from day 8 to 22 when SAEs, onset of chronic illness, AEs that necessitate a physician consultation and/or leading to withdrawal were collected; 1% to 2% of subjects reported AEs from day 23 to the end of the study when SAEs, onset of chronic illness, AEs leading to withdrawal were collected. Possibly or probably related AEs were reported by a similar percentage of subjects across the three groups: by 1% to 2% of subjects for days 1 to 7, by <1% of subjects for days 8 to 23, and by no subject for days 23 to 181.

No single AE was reported by  $\geq 2\%$  of subjects in either of the vaccine groups.

Three subjects in the CCI vaccine group, one subject in the IVV group, and one placebo subject withdrew from the study due to AEs that were not considered by the investigator to be related to the study vaccine.

There were four deaths (two in the CCI vaccine group, one in the IVV group, and one in the placebo group). All were unrelated to the study vaccine. The remaining 127 SAEs

(reported by 42 subjects in the CCI vaccine group, 35 subjects in the IVV group, and 38 subjects in the placebo group) were considered unrelated to the study vaccine as judged by the investigator.

#### **3.1.4. Subgroup Analysis**

(Post hoc) subgroup analyses of immunogenicity by gender or race (white vs. non-white) did not show any remarkable difference in immunogenicity between the genders or the race groups. Since this study was performed in individuals 18-49 years of age, no subgroup analysis was performed based on age.

(Post hoc) subgroup analyses of serious adverse events (SAE's) by gender or race (white vs. non-white) did not show any noteworthy difference in the distribution of SAE's between the genders or race groups. Since this study was performed in individuals 18-49 years of age, no subgroup analysis was performed based on age.

#### **3.1.5. Conclusions and Comments**

*Reviewer Comments:*

*The statistical reviewer was able to verify the numerical accuracy of the applicant's results for the tables presented in this review, as well as select secondary endpoints.*

*The primary efficacy endpoint, i.e., vaccine efficacy relative to placebo against vaccine-like strains, was achieved in the Per-Protocol (PP) and Modified-Intent-To-Treat (MITT) populations for the CCI vaccine.*

*The secondary efficacy endpoint of vaccine efficacy relative to placebo against non-vaccine-like strains, was not achieved by the CCI vaccine treated individuals. However, vaccine efficacy relative to placebo, regardless of the antigenic match of the strains, was achieved for the CCI vaccine in the PP and MITT populations.*

*Among the subset of subjects in the PP efficacy population with culture-confirmed influenza for the CCI vaccine group compared to the placebo group, there were no statistically significant differences in the secondary efficacy endpoints in terms of the number of days in bed, the number of inpatient/outpatient visits due to influenza illness, and the number of days of usual activity. However, if all subjects in the PP efficacy population are considered in the analysis, the differences between the CCI vaccine group compared to the placebo group for all these secondary efficacy endpoints appear to be statistically significant. It should be noted that this study was not powered to test the secondary endpoints nor are multiplicity adjustments made.*

*At day 22 post vaccination, both the criteria of seroconversion and seroprotection were met for all 3 strains by the CCI vaccine group. Conversely, none of the criteria were met against any of the strains by the placebo group, based on the CBER guidance for influenza vaccines.*

*In general, based on the analysis provided by the applicant and confirmed by the reviewing statistician, the CCI vaccine was safe and well tolerated.*

## **3.2 Evaluation of Efficacy and Safety: Study V58P4**

### **3.2.1 Study Design Overview**

Study V58P4 was “a Phase III, Observer-Blind, Randomized, Multi-Center Study to Evaluate Safety, Tolerability and Immunogenicity of a Single Intramuscular Dose of a Trivalent Subunit Influenza Vaccine Produced in Mammalian Cell Culture and of a Trivalent Subunit Influenza Vaccine Produced in Embryonated Hen Eggs, in Healthy Adult and Elderly Subjects in the 2004-2005 Influenza Season in Healthy Adult Subjects between Sept 2004 and May 2005.” This study involved 5 sites in Poland. This study was not performed under US-IND and was designed to meet European regulatory agency criteria for safety, tolerability, and immunogenicity based on age ranges (adults 18 to 60 years of age vs. adults  $\geq$  61 years of age) defined by the European regulatory agency.

#### **Primary Objectives for Efficacy**

##### *Immunogenicity Objectives*

To evaluate immunogenicity of a single 0.5 mL intramuscular (IM) injection of the cell (MDCK) culture-derived and egg-derived influenza subunit vaccines, in compliance with the requirements of the EMEA recommendations (CPMP/BWP/2490/00, CPMP/BWP/214/96).

#### **Secondary Objectives for Efficacy**

To demonstrate non-inferiority of immunogenicity (seroprotection, seroconversion, and sufficient increase in GMT) of a single 0.5 mL IM injection of the cell culture-derived influenza subunit vaccine versus a single 0.5 mL IM injection of the egg-derived influenza subunit vaccine.

#### **Safety Objective**

To evaluate safety and tolerability of a single 0.5 mL IM injection of the cell culture-derived and egg-derived influenza subunit vaccines.

## **Methodology**

This Phase III, randomized, active controlled, observer-blind study was planned to be 34 weeks in duration. At least 2650 subjects were to be randomly allocated in a 1:1 ratio to receive either cell culture-derived (test) or egg-derived (control) vaccine as a single IM injection of 0.5 mL in the deltoid muscle of preferably the non-dominant arm and were to be followed up for 6 months. The study subjects were stratified into 2 age groups at enrollment: the 18 to 60 years (adult) group was to comprise at least 1166 evaluable subjects and the  $\geq 61$  years (elderly) group was to comprise at least 1210 evaluable subjects. Two randomization lists (one for each age group) were provided to the investigator by Chiron Vaccines (now Novartis Vaccines) and were used only by unblinded study personnel.

Subject enrollment was over a period of 8 weeks. Each individual was enrolled only after an assessment by the investigator, based on medical history and a physical examination, to assess whether they met all inclusion criteria and none of the exclusion criteria. Subjects remained in the clinic for 30 minutes after vaccination to be monitored and evaluated for possible immediate hypersensitivity reactions. All study subjects were instructed to complete diary cards to record local reactions (i.e., ecchymosis, erythema, induration, swelling, and pain at injection site), systemic reactions (i.e., chills, malaise, myalgia, arthralgia, headache, sweating, and fatigue), axillary temperature, impact on normal daily life (stayed at home due to reaction), use of analgesic/antipyretic medication, and other adverse events (AEs), daily, for 7 days following vaccination (day 1 to day 7). All AEs and concomitant medications were collected during the 3 weeks following vaccination (day 1 - day 22). All serious AEs and/or AEs resulting in premature withdrawal from the study were collected throughout the study (up to week 26). If any AE remained unresolved by the end of the study, a clinical assessment was made by the investigator and Medical Monitor on whether continued follow-up of the AE was warranted. If a vaccine-related serious AE had occurred during the enrollment period, the investigator would have had to decide, after consultation with the chairman of the Ethics Committee and the Sponsor's Medical Monitor, whether to stop enrollment.

In total 10 mL of blood was collected by venipuncture immediately before vaccination (day 1) and 3 weeks afterwards (day 22) for immunogenicity analysis using the hemagglutination inhibition (HI) assay (i.e., antibodies against A/H1N1, A/H3N2 and B in serum samples were quantified with HI, using both cell culture- and egg-derived influenza antigens).

### **Number of subjects (planned and analyzed)**

A total of 583 evaluable adult subjects and 605 evaluable elderly subjects per group were necessary to test the null hypothesis. Considering 10% drop-outs, a total of approximately 2650 subjects (1300 adult subjects [650 in each vaccine group] and 1350 elderly subjects [675 in each vaccine group]) were to be enrolled.

In total 2654 subjects were enrolled into the study, of whom 1300 were aged 18-60 years and 1354 were aged 61 years and over. Nine subjects prematurely withdrew before the second blood draw. Five further subjects were excluded from the per-protocol analyses following major protocol deviations. Data from all the remaining 2640 subjects (1294 aged 18-60 years and 1346

aged 61 years and over) were analyzed for immunogenicity. All subjects were exposed to one of the study vaccines and therefore data from all 2654 subjects were included in at least one of the safety analyses.

### **Main criteria for inclusion and exclusion**

#### **Inclusion criteria**

- 1) 18 to 60 years of age or over 60 years of age
- 2) Mentally competent to understand the nature, the scope, and the consequences of the study
- 3) Able and willing to give written informed consent prior to study entry
- 4) Available for all the visits scheduled in the study
- 5) Residence in the study area
- 6) In good health

#### **Exclusion criteria**

- 1) Unable or unwilling to give written informed consent to participate in the study
- 2) Acute infectious disease
- 3) Any serious disease
- 4) Surgery planned during the study period

Additional information regarding the inclusion/exclusion criteria can be found in the medical officer's review.

### **Duration of study**

The study was to last approximately 8 weeks for the initial enrollment of subjects, then was to be followed by 26 weeks of observation for each enrolled/randomized study subject.

### **Criteria for evaluation**

#### **Immunogenicity**

##### ***Primary:***

The following serological assessments were considered for each strain in adult subjects aged 18 to 60 years, and all 3 assessments had to meet the indicated requirements assessed by the European Regulatory Agency (CPMP/BWP/2490/00, CPMP/BWP/214/96) at day 22:

- 1) number of seroconversions or significant increases in anti-hemagglutinin (HA) antibody titer >40%
- 2) mean geometric increase >2.5
- 3) the proportion of subjects achieving an HI titer  $\geq 40$  should be >70%

The following serological assessments were considered for each strain in elderly subjects aged over 60 years (i.e.,  $\geq 61$  years), and all 3 assessments had to meet the indicated requirements at day 22:

- A) number of seroconversions or significant increases in anti-HA antibody titer >30%
- B) mean geometric increase >2.0
- C) the proportion of subjects achieving an HI titer  $\geq 40$  should be >60%

### ***Secondary***

The following serological assessments were considered for each strain for all subjects and in both adult and elderly subjects according to the European recommendations for the non-inferiority criteria (CPMP/EWP/463/97):

- 1) the percentage of seroprotection in the test group is <10% lower than in the control group (i.e., the percentage of seroprotection of test group is not inferior to that of the control group if, for all 3 antigens, the lower limit of the two-sided 95% confidence interval (CI) of the difference in the percentages is greater than -10%).
- 2) the percentage of seroconversion or significant increases in the test group is <10% lower than in the control group (i.e., the percentage of seroconversion of test group is not inferior to that of the control group if, for all 3 antigens, the lower limit of the two-sided 95% CI of the difference in the percentages is greater than -10%).
- 3) the postvaccination test to licensed control group GMR ratio is >0.5 (i.e., the GMR of test group is not inferior to that of the control group if, for all 3 strains, the lower confidence limit of the two-sided 95% CI for ratio of GMRs at day 22 is greater than 0.5).

Note: All analyses were to be repeated, descriptively, for the subset of subjects who were not seroprotected at day 1 (i.e., who had HI titer <40).

### **Safety**

Numbers and percentages of subjects with reported local and systemic reactions (including fever: axillary temperature  $\geq 38^{\circ}\text{C}$ ), axillary temperature categorized as <38°C, 38 - <39°C, 39 – <40°C,  $\geq 40^{\circ}\text{C}$ , impact on normal daily life, and use of analgesic/antipyretic medication, as well as number of subjects with reported serious AEs and/or AEs resulting in premature withdrawal from the study, per vaccination group.

### **Statistical methods**

There was no pre-specified statistical null hypothesis associated with the primary immunogenicity objective, which was analyzed descriptively. However, the composite null hypothesis for the secondary immunogenicity objective states that for at least one strain the test group does not comply with the following non-inferiority assumptions:

- 1) the percentage of seroprotection rate in the test group is <10% lower than in the control group
- 2) the percentage of seroconversion rate or significant increases in the CCI group is <10% lower than in the control group
- 3) the post vaccination CCI to control group GMR ratio is >0.5.

The safety data are analyzed descriptively.

### **Statistical power and sample size considerations**

The sample size calculation was based on the objective of non-inferiority between “GMRs” (sufficient increase in GMTs), “seroprotection” and “seroconversion or significant increase.”

Assuming:

- 1) GMR standard deviations: 1.0 for both groups
- 2) Expected percentage of seroprotection rate equal to 80% for both vaccines in the adults
- 3) Expected percentage of seroprotection rate equal to 65% for both vaccines in the elderly
- 4) Expected percentage of seroconversion or significant increase equal to 60% in the adults
- 5) Expected percentage of seroconversion or significant increase equal to 50% in the elderly

In total 583 evaluable adult subjects per group and 605 evaluable elderly subjects per group were necessary to test the null hypothesis. Considering 10% of drop-outs, 1300 adults subjects were planned to be enrolled (650 in each vaccine group) and 1350 elderly subjects were planned to be enrolled (675 in each vaccine group) for a total of 2650 subjects. The study power to demonstrate non-inferiority by age groups was planned to be not inferior to 80%.

## **3.2.2 Results-Immunogenicity**

### **Immunogenicity results**

Only the HI assay results for the egg-derived antigens are presented here.

In total 1294 of the 1300 enrolled adult subjects and 1350 of the 1354 enrolled elderly subjects were included in the analysis of the per-protocol population. Within each age group and center demographic and other baseline characteristics were similarly distributed between the vaccination groups. In contrast to the adults, co-morbidity was very common in the elderly population (e.g., 32% [217 out of 678 elderly subjects] of the CCI and 33% [220 out of 676 elderly subjects] of the control groups had a history of disease of the circulatory system versus 7% for both adult vaccination groups).

The immune responses in:

Adults (18 to 60 years of age)

- 650 adult recipients of the MDCK-derived (CCI) vaccine
- 644 adult recipients the egg-derived (control) vaccine

Elderly ( $\geq$  61 years of age)

- 672 elderly recipients of the CCI vaccine
- 674 elderly recipients in the control group

were assessed (i.e., using the per protocol population) based on the European recommendation for harmonization of requirements of influenza vaccines (CPMP/BWP/214/96). All antibody determinations presented in CSR V58P4 Version 2 were performed by HI assay using egg-

derived viral antigen against the 3 strains used in the vaccine (i.e., A/New Caledonia/20/99 IVR-116, A/Fujian/411/2002-like type A/H3N2, and B/Shanghai/361/2002-like type). Seroprotection (i.e., HI titers >40), GMR (postvaccination/prevaccination HI titers), and seroconversion (HI titer <10 prevaccination and >40 postvaccination)/significant increase in titer (HI titer <10 prevaccination and at least 4-fold increase postvaccination) were used as the criteria for evaluation of the primary immunogenicity objective.

The following details the immunogenicity results based on the non-inferiority of the CCI product when compared to the comparator/control egg based product.

**Table 7** Non-inferiority of CCI to Control Vaccine

|   |   | Vaccine Group Difference/Ratio (95% CI)<br>(Test/CCI vs. Control) |                              |                   |                  |
|---|---|---|------------------------------|-------------------|------------------|
|   |   | Minimum<br>require  | HI using egg-derived antigen |                   |                  |
|   |   |   | A/H1N1                       | A/H3N2            | B                |
| Adults<br>(18 to 60<br>years of<br>age) | Seroprotection                            | >10% <sup>a</sup>   | 0% (-3%, 3%)                 | 0% (-1%, 2%)      | 0% (-3%, 3%)     |
|   | GMR                                       | >0.5 <sup>b</sup>   | 1.07 (0.9, 1.28)             | 0.85 (0.72, 0.99) | 1.14 (0.99, 1.3) |
|   | Seroconversion or<br>significant increase | >10% <sup>a</sup>   | 2% (-3%, 7%)                 | -1% (-6%, 4%)     | 4% (0%, 8%)      |
| Elderly<br>(≥ 61 years<br>of age)       | Seroprotection                            | >10% <sup>a</sup>   | -1% (-4%, 3%)                | -1% (-2%, 1%)     | 1% (-2%, 4%)     |
|   | GMR                                       | >0.5 <sup>b</sup>   | 0.96 (0.82, 1.12)            | 0.87 (0.74, 1.02) | 1.27 (1.11, 1.4) |
|   | Seroconversion or<br>significant increase | >10% <sup>a</sup>   | 0% (-6%, 5%)                 | 3% (-2%, 8%)      | 6% (2, 11)       |

<sup>a</sup> lower limit of the 95% CI of the difference in the percentages of seroprotection and seroconversion/significant increase of the Test/CCI minus control vaccination groups:

<sup>b</sup> lower limit of the 95% CI of the ratio in the GMRs of the Test/CCI to control.

### Adult subjects

#### Primary Objective

The seroprotection rates, GMRs, and seroconversions/significant titer increases in adult recipients of both the CCI and control vaccines were all above the CPMP/BWP/214/96 requirements (i.e., >70%, >2.5, >40%, respectively) for all 3 vaccine influenza strains as assessed by the HI assay using egg-derived viral antigens.

#### Secondary Objective

The percentages of adults who were seroprotected and either seroconverted or demonstrated a significant increase in titers 21 days after administration of the CCI vaccine were not inferior to those after vaccination with the control for any of the 3 influenza strains. The increases in titers induced by the CCI vaccine in the adult population were also not inferior to those induced by the control vaccine.

## **Pre-specified and Exploratory Analyses in Sub-populations**

All 3 CPMP/BWP/214/96 requirements for influenza vaccines were met by each sex in both vaccine groups. In addition, the subset of adults who were not seroprotected at baseline (HI titer < 40) also met all the requirements. In a subset of adults who had previously received influenza immunization, seroprotection against the A strains was achieved in high percentages (range, 91% to 100%) of recipients of both vaccines, even though not all seroconversion/significant increase criteria were attained against these strains, probably due to relatively high baseline titers.

In the adult population, the rates of co-morbidity were generally low (overall 45 subjects in the CCI group and 46 subjects in the control group [7% of both] had a history of disease of the circulatory system) and, accepting the limitation of the sample size, there was no evidence that the immune response to the CCI and control vaccines in adult subjects with a history of disease of the circulatory system differed from that seen for the total adult population (all 3 criteria were attained by subgroups with co-morbidities).

The immunogenicity results for adults, when analyzed using a two-way ANOVA model with factors for vaccine group and center, were generally similar, with the exception of the immune response to the A/H3N2 strain, where there appeared to be an advantage for recipients of the control vaccine.

### ***Elderly subjects (≥61 years of age)***

#### **Primary Objective**

The seroprotection rates, GMRs, and seroconversions/significant titer increases in elderly recipients of both the CCI and control vaccines were all above the CPMP/BWP/214/96 requirements (i.e., >60%, >2.0, >30%, respectively) for all 3 vaccine strains as assessed by the HI assay using egg-derived viral antigens.

#### **Secondary Objective**

The percentages of elderly subjects who were seroprotected and either seroconverted or demonstrated a significant increase in titers 21 days after administration of the CCI vaccine were not inferior to those after vaccination with the control for any of the 3 vaccine influenza strains. The increases in titers induced by the CCI vaccine in the elderly population were also not inferior to those induced by the control vaccine.

## **Pre-specified and Exploratory Analyses in Sub-populations**

All 3 European regulatory agency, CPMP/BWP/214/96 requirements for influenza vaccines were met by each sex for both vaccine groups. In addition, subsets of the elderly population who were not seroprotected at baseline, who had previously been vaccinated, or who had not previously received an influenza vaccination met all the requirements for all 3 strains.

In the elderly population, the percentages of subjects with diseases in their medical history were high. However, additional post hoc analyses performed in various subgroups did not provide additional insight into any trends that might differentiate immune responses.

The immunogenicity results for elderly subjects, when analyzed using a two-way ANOVA model with factors for vaccine group and center, were generally similar, with the exception of the immune response to the B strain, where there appeared to be an advantage for recipients of the CCI vaccine.

### 3.2.3 Results: Safety

All 1330 subjects (652 adults, 678 elderly) received a single dose of the cell culture-derived (CCI) vaccine and 1324 enrolled subjects (648 adults, 676 elderly) received a single dose of control vaccine.

A summary of the types of reactions observed, by age subgroup category (adults vs. elderly), can be seen in the following table.

**Table 8** Reactogenicity and other Adverse Events for both Adult (18-60 years of age) and Elderly Subjects ( $\geq 61$  years of age)

| Type of Reaction   |                                      | Adults (% of Adults 18-60 years of age) |                 | Elderly (% of Elderly $\geq 61$ years of age) |                 |
|--------------------|--------------------------------------|---|-----------------|---|-----------------|
|                    |                                      | CCI (N=652)                             | Control (N=648) | CCI (N=678)                                   | Control (N=648) |
| LOCAL/<br>SYSTEMIC | Any reaction                         | 262 (40%)                               | 263 (41%)       | 232 (34%)                                     | 216 (40%)       |
|                    | Local reaction                       | 209 (32%)                               | 200 (31%)       | 149 (22%)                                     | 121 (32%)       |
|                    | Systemic reaction                    | 144 (22%)                               | 147 (23%)       | 146 (22%)                                     | 147 (22%)       |
|                    | Other reaction                       | 48 (7%)                                 | 46 (7%)         | 47 (7%)                                       | 38 (6%)         |
| OTHER ADVERSE      | Any AE                               | 94 (14%)                                | 95 (15%)        | 101 (15%)                                     | 90 (13%)        |
|                    | At least possibly related AE         | 16 (2%)                                 | 25 (4%)         | 16 (2%)                                       | 16 (2%)         |
|                    | Serious AE                           | 7 (1%)                                  | 5 (1%)          | 19 (3%)                                       | 18 (3%)         |
|                    | At least possibly related serious AE | 0                                       | 0               | 0   | 0               |
|                    | Any death                            | 0                                       | 0               | 1 (<1%)                                       | 2 (<1%)         |

Additional descriptive analysis of adverse events can be seen in the Medical Officer's review.

#### *Adults*

Overall, the percentage of adult subjects reporting any selected local reaction, systemic reaction, or other indicators of reactogenicity was balanced between the CCI and control groups (40%

versus 41%). As expected, local reactions (32% CCI versus 31% control) were more frequently experienced than systemic reactions (22% CCI versus 23% controls) or other indicators of reactogenicity (7% of both groups). Although pain was the most common local reaction experienced by the adult population of both vaccination groups, its frequency appeared to be higher for recipients of the CCI vaccine (22% CCI versus 17% control). However, the severity profiles of pain were similar for adults of both vaccination groups, and severe pain was infrequent (<1% of both groups). Moreover, there was only a difference between the onset rates at 6 hours post vaccination, when peak onset was observed for both groups (i.e., 15% CCI versus 10% control). The overall reporting rates (i.e., onset and ongoing) of pain only differed between the CCI and control groups at 6 hours (15% versus 11%) and day 2 (15% versus 12%). Pain was transient and by day 4 was reported by only 2% of both groups. This dropped to <1% on each subsequent day. The incidence rates of all other local reactions were balanced between the adults of the vaccination groups (range 3%-16%).

The incidence rates of each systemic reaction were also balanced between the vaccination groups. Headache (12% of both groups), fatigue (11% of both groups), and malaise (11% of both groups) were the most common systemic reactions. Most systemic reactions were mild or moderate in severity with no more than 1% of either vaccination group experiencing systemic reactions of severe grade. The onset of systemic reactions generally peaked either at 6 hours (range <1% - 5%) or day 2 (range <1% - 4%). No more than 4% of either group daily reported each systemic reaction from day 4 to day 7. Fever (i.e., axillary temperature > 38°C) was reported by <1% of the test group and 1% of the control, none was severe (i.e., >40°C), 2% of both groups stayed at home due to a reaction, while in the CCI and control groups, respectively, 7% and 6% reported taking analgesic/antipyretic medication.

Other AEs, regardless of the assessment of relatedness to the study vaccine, were reported for 14% of adults in the CCI group and 15% in the control group. Most of these AEs were due to common illnesses expected for this population. Rhinitis was the most commonly reported AE in the adult population (24 [4%] CCI subjects and 31 [5%] control subjects). Only 2% of the CCI group and 4% of the control experienced AEs that were assessed as being possibly or probably related to the study vaccine. In both groups the most common possibly/probably related AE was rhinitis (experienced by 5 subjects [1%] in each vaccination group).

Within the adult population, no deaths occurred. Seven serious AEs were reported in the CCI group and 5 in the control group. All AEs resulted from hospitalizations and were not related to the study vaccines. No AE resulted in premature discontinuation of an adult subject.

## *Elderly*

Overall, the percentage of elderly subjects reporting any selected local reaction, systemic reaction, or other indicators of reactogenicity were similar between the CCI and control groups (34% versus 32%) although the incidence rate was less than that observed for the adult population. Systemic reactions were experienced by 22% for both groups whereas local reactions were experienced by 22% of the CCI group and 18% of the control. Other indicators of reactogenicity were experienced by 7% of the CCI and 6% of the control group. Although the overall incidence rate of local reactogenicity was slightly higher in the CCI group, this was accounted for by the higher rate of pain from the CCI vaccine (9% CCI versus 5% of control). The percentages of elderly subjects experiencing pain, however, were lower than for adults. The severity profiles of pain were similar for both vaccination groups and severe pain was not reported at all by the elderly. Moreover, there was only a difference in onset rates at 6 hours post vaccination, when peak onset was observed for both groups (i.e., 6% CCI versus 3% control), and day 2 (3% CCI versus 1% control). Reporting rates of pain differed between the CCI and control groups at 6 hours (6% versus 3%), day 2 (7% versus 3%), and day 3 (4% versus 2%). Pain was transient, and on each day from day 4 to day 7 no more than 1% of either vaccination group reported pain. The incidence rates of all other local reactions were balanced between the elderly subjects of the vaccination groups (range 3% - 11%).

The incidence rates of each systemic reaction were balanced between the vaccination groups. Headache, fatigue, and malaise were the most common systemic reactions and in both vaccination groups were reported by between 10% and 12% of subjects. Most systemic reactions were mild or moderate in severity with no more than 1% of either vaccination group experiencing those of severe grade. The onset of systemic reactions generally peaked either at 6 hours (range <1% - 5%) or day 2 (range <1% - 4%). No more than 2% of the CCI group and 3% of the control group reported each systemic reaction on day 7. Fever (i.e., axillary temperature > 38°C) was reported by 1% of both groups, none was severe (i.e., >40°C). In the CCI and control groups 3% and 2%, respectively, stayed at home due to a reaction while 5% and 4% reported taking analgesic/antipyretic medication, also respectively.

Other AEs, regardless of the assessment of relatedness to the study vaccine, were reported for 15% of elderly subjects in the CCI group and 13% in the control group. These were similar incidence rates to those of adults. Most of these AEs were due to common illnesses expected within this population. Rhinitis was the most commonly reported AE in the elderly population (3% in both vaccination groups). Only 2% of both vaccine groups experienced AEs that were assessed as being possibly or probably related to the study vaccine. In both groups the most common possibly/probably related AE was rhinitis (< 1% of each group).

Within the elderly population, 3 deaths occurred (1 CCI, 2 control), all of which were unrelated to the study vaccines. One of the subjects who died (control) also experienced 2 other serious AEs. Forty-four other serious AEs were reported in 34 elderly subjects (18 CCI subjects, 16 control subjects). All these serious AEs involved hospitalizations (a criterion for categorization of seriousness) and all were deemed not related to the study vaccines. The most commonly effected system organ class by serious AEs was “cardiac disorders,” as expected by the medical

history of the elderly subjects. No AE, other than the 3 deaths reported above, resulted in premature discontinuation of an elderly subject in the study.

### 3.2.4. Subgroup Analysis

(Post hoc) subgroup analyses of immunogenicity by gender, age (18 to < 65 years of age vs ≥ 65 years of age), or race (white vs. non-white) did not show any remarkable difference in immunogenicity between the gender, age, or the race groups, with all groups meeting criteria for immunogenicity. A summary of the immunogenicity non-inferiority comparisons stratified by the age grouping used by the US (<65 years of age versus ≥ 65 years of age) can be seen below. These results are similar to the results observed when examining the European stratification of elderly utilizing 60 years of age as the cut point.

**Table 9** Non-inferiority of CCI to Control Vaccine for both Adults and Elderly Subjects utilizing a definition of elderly to consist of those ≥65 years of age

|                              |  | Vaccine Group Difference/Ratio (95% CI)<br>(CCI vs. Control) |                              |                   |                   |
|------------------------------|--|--|------------------------------|-------------------|-------------------|
|                              |  | Minimum requirement for non-inferiority                      | HI using egg-derived antigen |                   |                   |
|                              |  |  | A/H1N1                       | A/H3N2            | B                 |
| Adults<br>< 65 years of age  | Seroprotection                         | > -10% <sup>a</sup>  | 0% (-3%, 3%)                 | 0% (-1%, 2%)      | 0% (-3%, 3%)      |
|                              | Seroconversion or significant increase | > -10% <sup>a</sup>  | 1% (-3%, 7%)                 | -1% (-6%, 4%)     | 4% (0%, 8%)       |
|                              | GMT Ratio                              | ≥ 0.67   | 0.97 (0.85, 1.11)            | 0.93 (0.84, 1.02) | 1.14 (1.02, 1.27) |
| Elderly<br>≥ 65 years of age | Seroprotection                         | > -10% <sup>a</sup>  | 1% (-3%, 4%)                 | -1% (-2%, 1%)     | 0% (-4%, 4%)      |
|                              | Seroconversion or significant increase | > -10% <sup>a</sup>  | 0% (-6%, 5%)                 | 4% (-2%, 8%)      | 6% (1, 11)        |
|                              | GMT Ratio                              | ≥ 0.67   | 1.06 (0.92, 1.22)            | 0.97 (0.84, 1.12) | 1.28 (1.1, 1.48)  |

<sup>a</sup> lower limit of the 95% CI of the difference in the percentages of seroprotection and seroconversion/significant increase of the CCI minus control vaccination groups:

(Post hoc) subgroup analyses of serious adverse events (SAE's) by gender, age, or race (white vs. non-white) did not show any noteworthy difference in the distribution of SAE's between the gender, age, or race groups. A summary of the reactions observed stratified by the age grouping used by the US (<65 years of age versus ≥ 65 years of age) can be seen below. These results are similar to the results observed when examining the European stratification of elderly utilizing 60 years of age as the cut point.

**Table 10** Reactogenicity and other Adverse Events for both Adult and Elderly Subjects utilizing a definition of elderly to consist of those ≥ 65 years of age

| Type of Reaction             | Adults (% of Adults) |                    | ≥65 years of Age (% of Elderly) |                    |
|------------------------------|----------------------|--------------------|---------------------------------|--------------------|
|                              | CCI<br>(N=820)       | Control<br>(N=813) | CCI<br>(N=509)                  | Control<br>(N=483) |
| Any AE                       | 114 (14%)            | 121 (15%)          | 81 (16%)                        | 65 (14%)           |
| At least possibly related AE | 18 (2%)              | 27 (3%)            | 14 (3%)                         | 14 (3%)            |
| Serious AE                   | 9 (1%)               | 8 (1%)             | 17 (3%)                         | 15 (3%)            |
| At least possibly related    | 0                    | 0                  | 0                               | 0                  |
| Any death                    | 0                    | 0                  | 1 (<1%)                         | 2 (<1%)            |

### 3.2.5. Conclusions and Comments

#### *Reviewer Comments:*

*Both the post-hoc primary and secondary immunogenicity objectives were met by both adults and the elderly as assessed by the HI assay using egg-derived viral antigens. Within the original protocol, there were no pre-specified criteria that defined success with respect to immunogenicity objectives, and only descriptive analyses were to be performed. However, CBER agreed to the use of this study to support the desired claim during the pre-BLA meeting and asked the company to reanalyze the data according to the US definition.*

*The CCI vaccine appears to be as safe as the control vaccine, based on observed Adverse Events and systemic and local reactions. The reactogenicity of both CCI and control vaccines was similar within each age group. Only pain, of which over 99% was mild or moderate, was more frequently experienced by recipients of the CCI than the control vaccine (adults 22% versus 17%; elderly 9% versus 5%, respectively). However, the difference in incidence rates was confined to a maximum of 2 days after injection and was deemed not clinically relevant. Most other AEs reported by this study population were considered unrelated to the vaccines administered in this study. Those judged to be possibly or probably related to vaccination were experienced infrequently and were either ongoing local/systemic reactions (i.e., past day 7) or other common side-effects of vaccination. The 3 serious AEs leading to death and 58 other serious AEs reported during this study predominantly occurred in the elderly population: all were deemed unrelated to the study vaccines. The incidence rates of serious AEs were as expected for this elderly population, where co-morbidities were very common.*

### 3.3 Evaluation of Efficacy and Safety: Study V58P9

#### 3.3.1. Design Overview

Study V58P9 was “A Phase III, Randomized, Controlled, Observer-Blind, Multi-Center Study to Evaluate Safety, Tolerability and Immunogenicity of a Single Intramuscular Dose of Three Lots of a Trivalent Subunit Influenza Vaccine Produced in Mammalian Cell Culture Or of a Trivalent Subunit Influenza Vaccine Produced in Embryonated Hen Eggs, in Healthy Adult

*Subjects Aged 18 to <61 Years in the 2005-2006 Influenza Season.*” This study involved approximately 1200 subjects randomized to 3 lots of the cell-derived vaccine and one lot of the egg-derived vaccine in a 2:2:2:1 ratio within two (2) sites in Lithuania.

The primary safety objectives were:

- to evaluate the safety and tolerability of Flucelvax (CCI) as compared to Agriflu (IVV) three weeks after a single dose of study vaccine, and
- to collect additional safety data such as SAEs, medically attended AEs, and AEs resulting in premature study discontinuation for six months post vaccination.

The primary immunogenicity objective was to evaluate the immunogenicity of the two study vaccines and of each vaccine lot three weeks after a single 0.5 mL intramuscular injection, by the measurement of strain-specific HI tests according to the current CHMP criteria (CPMP/BWP/214/96). Additionally, although there were safety and immunogenicity objectives, the applicant stated in the Clinical Study Report that the study was “primarily designed to descriptively assess safety.” This study was not performed under US-IND but was submitted to the Agency within the BLA as a post-hoc lot-to-lot consistency study. Due to irregularities with the data from Site 2 of this study, this review considered the data with and without Site 2 data included.

### **3.3.3 Results: Immunogenicity**

In total 1017 of the 1200 enrolled adult subjects were included in the analysis of the per-protocol population. Baseline characteristics/demographics were similarly distributed between the vaccination groups.

The immune responses were assessed (i.e., using the per- protocol population) based on the European recommendation for harmonization of requirements for influenza vaccines (CPMP/BWP/214/96) 21 days after vaccine administration. For all strains and for both endpoints of seroprotection rate (SPR) and seroconversion rate (SCR), CCI also met the CBER criteria for immune responses (i.e.,  $SPR \geq 70\%$  and  $SCR \geq 40\%$  for adults aged 18-64)

A summary of the immunogenicity responses can be observed in the following table, which compares the results of both sites together to Site 1 only.

**Table 11** Immunogenicity Responses including Seroconversion and Seroprotection Rates for both Sites and Site 1 only.

|                                     | Overall Population |                  |                 | Site 1 Only     |                 |                 |
|-------------------------------------|--------------------|------------------|-----------------|-----------------|-----------------|-----------------|
| Day 22                              | H1N1               | H3N2             | B               | H1N1            | H3N2            | B               |
| <b>Seroconversion Rate (95%CI)</b>  |                    |                  |                 |                 |                 |                 |
| <b>CCI</b>                          | 81%<br>(79-83%)    | 83%<br>(80-86%)  | 78%<br>(76-81%) | 81%<br>(78-84%) | 80%<br>(77-83%) | 80%<br>(77-83%) |
| <b>IVV</b>                          | 77%<br>(70-83%)    | 88%<br>(82-93%)  | 70%<br>(63-77%) | 77%<br>(69-84%) | 88%<br>(82-93%) | 71%<br>(64-78%) |
| <b>Seroprotection Rate (95% CI)</b> |                    |                  |                 |                 |                 |                 |
| <b>CCI</b>                          | 94%<br>(92-96%)    | 93%<br>(91%-95%) | 91%<br>(89-93%) | 96%<br>(94-98%) | 92%<br>(90-94%) | 93%<br>(91-95%) |
| <b>IVV</b>                          | 95%<br>(91-98%)    | 96%<br>(92-99%)  | 88%<br>(82-92%) | 94%<br>(90-97%) | 96%<br>(92-99%) | 89%<br>(85-93%) |

When examining the seroconversion rates, no distinct pattern emerges for either the strain of influenza included and studied or the inclusion or exclusion of the Site 2 data. All treatment groups are shown to be consistently above the CBER threshold for all influenza strains.

Analysis of the three lots was performed by the sponsor. Results are shown in the following table.

**Table 12** Summary of Seroprotection and Seroconversion/Significant Increase in the Overall Population and Excluding Site 2

| Strain | Criteria   | Percentages of subjects (95% CI) |                |                |                |                 |                             |                |                |                |                |
|--------|--|----------------------------------|----------------|----------------|----------------|-----------------|-----------------------------|----------------|----------------|----------------|----------------|
|        |  | Overall population               |                |                |                |                 | Population excluding site 2 |                |                |                |                |
|        |  | cTIV<br>N=1017                   | Lot A<br>N=339 | Lot B<br>N=337 | Lot C<br>N=341 | eTIV-a<br>N=168 | cTIV<br>N=589               | Lot A<br>N=198 | Lot B<br>N=193 | Lot C<br>N=198 | eTIV-a<br>N=98 |
| A/H1N1 | Prevaccination Seroprotection <sup>a</sup>                       | 29<br>(26-32)                    | 29<br>(24-34)  | 31<br>(26-36)  | 27<br>(22-32)  | 30<br>(24-38)   | 36<br>(32-40)               | 36<br>(29-43)  | 38<br>(31-46)  | 34<br>(27-41)  | 38<br>(28-48)  |
|        | Postvaccination Seroprotection                                   | 94<br>(92-95)                    | 95<br>(92-97)  | 93<br>(90-95)  | 94<br>(91-96)  | 95<br>(91-98)   | 96<br>(94-98)               | 97<br>(94-99)  | 97<br>(93-99)  | 94<br>(90-97)  | 97<br>(91-99)  |
|        | Seroconversion <sup>b</sup> or significant increase <sup>c</sup> | 81<br>(79-84)                    | 80<br>(76-84)  | 79<br>(74-83)  | 85<br>(80-88)  | 77<br>(70-83)   | 81<br>(78-84)               | 80<br>(74-86)  | 81<br>(75-86)  | 82<br>(76-87)  | 76<br>(66-84)  |
| A/H3N2 | Prevaccination Seroprotection <sup>a</sup>                       | 24<br>(22-27)                    | 19<br>(15-23)  | 26<br>(22-31)  | 28<br>(23-33)  | 27<br>(20-34)   | 26<br>(22-30)               | 19<br>(14-25)  | 31<br>(24-38)  | 28<br>(22-35)  | 28<br>(19-37)  |
|        | Postvaccination Seroprotection                                   | 93<br>(91-95)                    | 94<br>(90-96)  | 93<br>(90-95)  | 93<br>(90-96)  | 96<br>(92-99)   | 92<br>(90-94)               | 92<br>(88-96)  | 93<br>(88-96)  | 91<br>(86-95)  | 97<br>(91-99)  |
|        | Seroconversion <sup>b</sup> or significant increase <sup>c</sup> | 83<br>(80-85)                    | 85<br>(81-89)  | 82<br>(77-86)  | 81<br>(77-85)  | 88<br>(82-93)   | 80<br>(77-83)               | 84<br>(78-89)  | 79<br>(72-84)  | 78<br>(71-83)  | 88<br>(80-94)  |
| B      | Prevaccination Seroprotection <sup>a</sup>                       | 23<br>(20-26)                    | 21<br>(16-25)  | 27<br>(22-32)  | 22<br>(17-26)  | 21<br>(15-28)   | 27<br>(23-31)               | 25<br>(19-32)  | 31<br>(25-38)  | 25<br>(19-31)  | 31<br>(22-41)  |
|        | Postvaccination Seroprotection                                   | 91<br>(89-93)                    | 90<br>(87-93)  | 91<br>(88-95)  | 91<br>(88-94)  | 88<br>(82-92)   | 93<br>(91-95)               | 92<br>(88-96)  | 94<br>(90-97)  | 93<br>(89-96)  | 93<br>(86-97)  |
|        | Seroconversion <sup>b</sup> or significant increase <sup>c</sup> | 78<br>(76-81)                    | 78<br>(73-82)  | 78<br>(74-83)  | 79<br>(74-83)  | 70<br>(63-77)   | 80<br>(77-83)               | 79<br>(72-84)  | 81<br>(75-87)  | 80<br>(74-85)  | 70<br>(60-79)  |

Source: Table 11.4.1-2, Table 11.4.1-3, Table 11.4.1-4 of full CSK version 2, Table 14.2.1.1.1, Table 14.2.1.1.6, Table 14.2.1.2.1, Table 14.2.1.2.6 of addendum 2; <sup>a</sup> Seroprotection = HI titers  $\geq 40$ ; <sup>b</sup> Seroconversion is defined as HI titer  $< 10$  prevaccination and  $\geq 40$  postvaccination; <sup>c</sup> Significant increase is defined as HI titer  $\geq 10$  prevaccination and  $\geq 4$ -fold HI titer increase postvaccination; bold: meet relevant CHMP criterion.

Note: this table is copied directly from the sponsor provided V58P9 Amendment 2 page 20 of 1082 dated 28 Feb 12.

Considering these results, the post-hoc analysis to demonstrate lot-to-lot consistency appears to meet the CHMP and US-FDA-CBER criterion both for Seroconversion and Seroresponse for all strains, when considering the overall populations. However, it is important to note that the applicant acknowledges that although the study primary immunogenicity objective was to evaluate the 3 lots against the CHMP criteria, no formal statistical hypotheses were pre-specified for the demonstration of lot-to-lot consistency.

The analysis to demonstrate lot-to-lot consistency based on GMT Ratios comparing different lots can be examined in the following table.

**Table 13** Lot-to-Lot Consistency Immunogenicity Results Overall Population and Excluding Site 2—Assessment of Equivalence of Three CCI Vaccine Lots

|        | cTIV <sup>c</sup> Vaccine Lots Day 22 GMT <sup>d</sup> ratios (95% CI) |                     |                                   |                                   |                     |                     |
|--------|--|---------------------|-----------------------------------|-----------------------------------|---------------------|---------------------|
|        | Overall population   |                     |                                   | Population excluding site 2       |                     |                     |
|        | Lots A vs. B   | Lots A vs. C        | Lots B vs. C                      | Lots A vs. B                      | Lots A vs. C        | Lots B vs. C        |
| A/H1N1 | 1.02<br>(0.83-1.25)  | 0.84<br>(0.69-1.04) | 0.83<br>(0.67 <sup>a</sup> -1.02) | 1.07<br>(0.83-1.38)               | 1.07<br>(0.83-1.37) | 0.99<br>(0.77-1.28) |
| A/H3N2 | 0.97<br>(0.81-1.17)  | 1.1<br>(0.92-1.32)  | 1.13<br>(0.94-1.36)               | 1.02<br>(0.81-1.3)                | 1.1<br>(0.87-1.4)   | 1.08<br>(0.85-1.37) |
| B      | 0.82<br>(0.69-0.97)  | 0.93<br>(0.78-1.1)  | 1.13<br>(0.96-1.34)               | 0.83<br>(0.67 <sup>b</sup> -1.02) | 1.02<br>(0.83-1.25) | 1.23<br>(1-1.51)    |

Source: Table 14.2.1.3.6, Table 14.2.1.3.2; <sup>a</sup> 0.67126 = lower limit of the two-sided 95% CI for day 22 GMT ratio of lot B over lot C for the A/H1N1 strain; <sup>b</sup> 0.67439 = lower limit of the two-sided 95% CI for day 22 GMT ratio of lot A over lot B for the B strain; <sup>c</sup> cTIV = cell culture-derived influenza vaccine; <sup>d</sup> GMT = geometric mean titer.

When considering the lot-to-lot consistency comparisons for all three strains based on only Site 1, it can be seen that 2 of the 3 strains meet the US-FDA-CBER standards based on GMT ratios. However, in the population including only Site 1, the upper limit of the 95% CI for the B strain was 1.51, which only narrowly missed the upper limit of 1.50 defined by CBER.

### 3.3.3 Results: Safety

#### Evaluation of Safety

All the safety analyses consisted of descriptive statistics only. The primary analysis of safety was based on the total vaccinated ITT cohort. Assessments of safety including local and systemic reactogenicity, as well as collection of adverse events, were performed through day 22. The follow-up continued for a total of approximately 26 weeks to assess long-term safety.

#### **Safety Results**

A total of 1028 subjects received a single dose of the cell culture-derived (CCI) vaccine and 171 subjects received the comparator IVV vaccine in both Site 1 and Site 2. After excluding Site 2, a total of 599 subjects received a single dose of the cell culture derived (CCI) vaccine and 100 subjects received a single dose of the comparator IVV vaccine.

One death occurred in this study in Site 1. Further discussion of this subject can be found in the medical officer’s review.

The following table presents the percentage of subjects with local and systemic reactions noted within the first 22 days post-vaccination.

**Table 14** Reactogenicity Responses to CCI and IVV vaccines for both Sites and Site 1 only.

|                 | Overall Population |              | Site 1 Only Population |              |
|-----------------|--------------------|--------------|------------------------|--------------|
|                 | CCI<br>N=1028      | IVV<br>N=171 | CCI<br>N=599           | IVV<br>N=100 |
| <b>Any</b>      | 421 (41%)          | 63 (37%)     | 239 (40%)              | 35 (35%)     |
| <b>Local</b>    | 298 (29%)          | 42 (25%)     | 131 (22%)              | 16 (16%)     |
| <b>Systemic</b> | 257 (25%)          | 39 (23%)     | 167 (28%)              | 29 (29%)     |

The percentages of subjects reporting any, local, or systemic reactions appeared to be slightly higher for the CCI treatment group than the IVV group when considering subjects in both Site 1 and Site 2 combined. This trend is similar when excluding Site 2, except for systemic reactions in which the IVV subjects have a slightly higher rate.

A summary of the types of reactions observed can be seen in the following table for both the overall population as well as the population excluding Site 2.

**Table 15** Types of Reactions Observed in each treatment group (CCI and IVV) for both Sites and Site 1 only.

|                   | Overall Population |              | Site 1 Only Population |              |
|-------------------|--------------------|--------------|------------------------|--------------|
|                   | CCI<br>N=1028      | IVV<br>N=171 | CCI<br>N=599           | IVV<br>N=100 |
| <b>Pain</b>       | 123 (12%)          | 14 (8%)      | 78 (13%)               | 10 (10%)     |
| <b>Erythema</b>   | 205 (20%)          | 31 (18%)     | 66 (11%)               | 8 (8%)       |
| <b>Induration</b> | 113 (11%)          | 19 (11%)     | 30 (5%)                | 6 (6%)       |
| <b>Ecchymosis</b> | 41 (4%)            | 10 (6%)      | 18 (3%)                | 5 (5%)       |
| <b>Swelling</b>   | 72 (7%)            | 14 (8%)      | 24 (4%)                | 4 (4%)       |

The most frequently reported solicited local reaction for both the CCI and IVV vaccines was Erythema, when both sites were included. Excluding Site 2, the most common reaction became pain for both the CCI and IVV vaccines. Additionally, when considering these reactions it is of note that by excluding Site 2, the rates of reactions generally decreased for both treatment groups.

### **3.3.4. Subgroup Analysis**

(Post hoc) subgroup analyses of immunogenicity by gender did not show any remarkable difference in immunogenicity between the genders. Since this study was performed in Caucasian individuals 18-60 years of age, no subgroup analysis was performed based on age or race.

(Post hoc) subgroup analyses of serious adverse events (SAEs) by gender did not show any noteworthy difference in the distribution of SAEs between the genders. Since this study was performed in Caucasian individuals 18-60 years of age, no subgroup analysis was performed based on age or race.

### **3.3.5. Statistical Comments**

*Reviewer Comments: In summary the reviewing statistician has the following comments related to this study, Study V58P9.*

*1) In the Clinical Study Report, the applicant states that the study was designed primarily to provide a descriptive assessment of safety and not as a lot-to-lot consistency study. Thus, the study was not designed to examine lot consistency, but post-hoc analyses for lot consistency were conducted. The nominal significance/p-value needs to be interpreted with caution since it does not account for multiple-testing Type I error issues associated with also performing other secondary hypothesis tests that were actually planned and prioritized over it.*

*2) Regarding some irregularities at Site 2, the applicant acknowledges that “some activities performed at this site during the earlier VP58 study for Optaflu was [sic] suboptimal (probably due to speed of enrollment and lack of adequate resources)” (page 14 of 1082 V58P9 Amendment 2 dated 28 Feb 12). The data integrity issues are common for both Site 1 as well as Site 2. It is unclear how data were collected and verified for either the disqualified site as per the applicant (Site 2) or Site 1, considering on average 500 subjects were enrolled within 6 days and apparently only one nurse collected and transported all blood samples within a 6-day window.*

*Further details regarding data integrity issues within Study V58P9 can be found in the clinical review.*

Additional Phase I and Phase II studies were provided in this submission. No unusual trends with respect to safety, tolerability, or efficacy were noted. Summaries of these studies can be found in the Medical Officer’s review.

## **4. SUMMARY AND CONCLUSIONS**

### **4.1 Statistical Issues and Collective Evidence**

*This BLA submission included the results of 7 Phase I, Phase II, and Phase III studies to examine the safety, tolerability, immunogenicity, and efficacy of a novel cell-culture derived vaccine in adults and one study examining pediatric subjects. The majority of these studies were not performed under US-IND, and only one Phase III study included in this submission was designed from inception to test any pre-specified hypothesis related to efficacy and immunogenicity. This pivotal Phase III study, V58P13, performed under US-IND did meet the pre-specified criteria establishing the efficacy and immunogenicity of this product: Flucelvax®/CCI.*

*The data suggest that this cell-culture seasonal influenza vaccine may have a reasonable safety profile, with comparable trends of adverse events to other seasonal influenza vaccines*

*The trends observed within this BLA submission provide supportive evidence that Flucelvax®/CCI is efficacious in preventing seasonal influenza and provides adequate immune response in the adult and elderly populations, based on the FDA Guidance for Influenza Vaccines.*

*The applicant's written assessment of the various Flucelvax®/CCI studies,*

*V58P1 (Germany)*

*V58P2 (New Zealand)*

*V58P4 (Poland)*

*V58P4E1 (Poland)*

*V58P5 (US)*

*V58P9 (Lithuania)*

*V58P12 (US, Finland, Lithuania, Hungary, Romania, Italy, Croatia)*

*V58P13 (US, Finland, Poland)*

*included in this BLA submission suggests that the Flucelvax®/CCI vaccine has a reasonable risk/benefit profile. Furthermore, analyses performed by the Agency statistician (of select primary safety endpoints; efficacy data provided within this submission, particularly the Phase III study performed under US-IND; and sensitivity analyses not presented) support the applicant's assertion that this product has an acceptable safety, efficacy, and immunogenicity profile.*

*Several of the studies provided in this submission were not under US-IND. The immunogenicity endpoints were later revised (post-hoc) to become primary endpoints in support of US licensure based on criteria included within the FDA Guidance for Influenza Vaccines.*

## **4.2 Conclusions and Recommendations**

*Based on efficacy and immunogenicity endpoint data and an acceptable safety profile provided within BLA 125408 amendment 0, and consideration of the totality of the evidence related to the novel Cell-Culture Derived Influenza Vaccine, I recommend that Flucelvax®/CCI be considered for approval in adults 18 + years of age because of potential clinical benefits that outweigh known risks.*

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