London, 21.06.2007
Product name: **Zostavax**
Procedure No. EMEA/H/C/000674/II/0003

SCIENTIFIC DISCUSSION

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3.1. Introduction

ZOSTAVAX is a live attenuated vaccine containing Varicella-zoster virus1, Oka/Merck strain, (live, attenuated, not less than 19400 Plaque-Forming Units (PFU)). ZOSTAVAX was developed for prevention of herpes zoster (HZ) and herpes zoster-related post herpetic neuralgia in individuals 60 years and older as a single-dose vaccine.

The Marketing Authorisation of ZOSTAVAX was granted in May 2006; however the product has not been launched in any Member State of the European Union yet.

A manufacturing change for ZOSTAVAX from a frozen to a refrigerator-stable formulation (Variation EMEA/H/C/000674/II/0002) was adopted by the CHMP in November 2006.
The currently authorised "refrigerated formulation" of ZOSTAVAX is a sterile lyophilised product prepared by formulating the attenuated Oka/Merck VZV strain propagated in MRC-5 cell culture. Sterile diluent is provided for reconstitution. As before, the vaccine is formulated to contain 19,400 or more plaque-forming units (PFU) of VZV per dose at expiry.

The modification sought in this variation was to expand the indication of ZOSTAVAX to individuals ≥ 50 years of age for the prevention of HZ and its complications.

Despite the availability of antiviral agents to treat HZ and a variety of medications and other therapies to help control the associated pain, HZ and its complications represent a large and growing medical problem among adults 50 years of age or older.

The MAH estimated that routine vaccination beginning at 50 years of age could increase by at least 50% the number of HZ cases that could be prevented each year, compared with routine vaccination beginning at 60 years of age. Preventing these cases would also prevent the corresponding burden of HZ complications, including PHN.

3.2. Clinical efficacy

The efficacy of ZOSTAVAX was previously demonstrated in Protocol 004 ("Shingles Prevention Study", "SPS"), a randomised, double-blind, placebo-controlled, multicentre efficacy study in adults ≥ 60 years of age. Protocol 004 was included as pivotal study in the initial application for the Marketing Authorisation. The data from this study demonstrated that compared with placebo, ZOSTAVAX was significantly efficacious in preventing HZ and HZ-associated pain, including PHN.

Protocol 010 evaluated in this variation procedure was a randomised, controlled, double-blind, multicentre study to assess the safety, tolerability, and immunogenicity of the refrigerated formulation zoster vaccine compared with the frozen formulation.

Protocol 011 evaluated in this variation procedure was a randomised, controlled, double-blind, multicentre study to assess the safety, tolerability, and immunogenicity of ZOSTAVAX administered concomitantly versus sequentially with inactivated influenza vaccine. Administration of ZOSTAVAX and placebo was blinded, but all subjects received open-labelled influenza vaccine on day 1.

Clinical studies

In Protocol 010, a total of 367 HZ history-negative adults 50 years of age and older were stratified 1:2 by age (50 to 59 years of age and ≥60 years of age, respectively) and were randomised in a 1:1 ratio on day 1 to receive one dose of either the refrigerated formulation zoster vaccine (44,846 PFU/0.65 ml) or the frozen formulation zoster vaccine (56,845 PFU/0.65 ml). Serum samples were obtained prior to vaccination on day 1 and at week 4 post vaccination, and were tested for VZV antibody levels using glycoprotein enzyme-linked immunosorbent assay (gpELISA). The VZV antibody response was also

measured by gpELISA at 6 weeks post vaccination. Other assays measuring the VZV-specific cell-mediated immune (CMI) - response elicited by vaccination have been used in other clinical studies in the development program for ZOSTAVAX as well as the CMI Substudy of the Shingles Prevention Study. Although these assays correlated somewhat with protection against HZ, the vaccine effect on the reduction of HZ incidence was best reflected by the measurement of the VZV antibody response by gpELISA (titer and fold rise from prevaccination). In the CMI Substudy of the Shingles Prevention Study, a regression analysis showed that the increase in gpELISA titres at 6 weeks post vaccination was associated with a significant reduction in the risk of developing HZ ($p<0.001$).

In Protocol 011, a total of 763 HZ history-negative adults 50 years of age and older were stratified 1:2 by age (50 to 59 years of age and ≥60 years of age, respectively) and were randomised in a 1:1 ratio to receive either ZOSTAVAX concomitantly with influenza vaccine on day 1 and placebo on week 4 or influenza vaccine with placebo on day 1 and ZOSTAVAX at week 4. In this study the frozen formulation of ZOSTAVAX was administered at a potency of 58.331 PFU/0.65ml. Approximately 75 % of the subjects were enrolled in the United States and 25 % of the subjects were enrolled in Europe. The VZV antibody response was measured by gpELISA at 4 weeks post vaccination. Other assays measuring the VZV-specific CMI response elicited by vaccination have been used in other clinical studies in the development program for ZOSTAVAX, as well as the CMI Substudy of the Shingles Prevention Study. Although these assays correlated with protection against HZ, the vaccine effect on the reduction of HZ incidence in the CMI Substudy of the Shingles Prevention Study was best reflected by the measurement of the VZV antibody response by gpELISA (titer and fold rise from prevaccination).

Serum samples were obtained prior to vaccination on day 1, week 4 and at week 8 post vaccination, and were tested for VZV antibody levels using gpELISA.
For strain-specific influenza antibody responses by haemagglutinin inhibition sera were obtained at day 1 prior vaccination and at week 4, which were tested at Focus Diagnostics, Inc., Cypress, California, USA.

Initial studies of ZOSTAVAX also measured immune responses at 6 weeks post vaccination. Since safety follow-up was shortened to 28 days post vaccination in Protocol 010 and subsequent studies, including Protocol 011, the immunogenicity sample collection was combined with the review of Vaccine Report Card (VRC) in a single post vaccination visit, to simplify study procedures for the subjects and study sites. In addition, the antibody responses to influenza were assessed at 28 days post vaccination by HAI as previously established in influenza vaccine studies.

Methods

Combined analysis of studies 010 and 011 and bridging of immunological data to demonstrate efficacy

The immunogenicity data presented in this application were derived from an integrated report, which analysed combined immunogenicity data from two clinical studies, Protocol 010 and Protocol 011. These data were presented to demonstrate that ZOSTAVAX induces a VZV antibody response in subjects 50 to 59 years of age that is noninferior to that in subjects ≥ 60 years of age, and thereby provides an immunological bridge to the vaccine efficacy demonstrated in the SPS in subjects ≥ 60 years of age.

In the integrated report, the analyses of the varicella-zoster virus (VZV) antibody responses to ZOSTAVAX among subjects 50 to 59 years of age in comparison with those in subjects 60 years of age or older were presented. The immunogenicity data from the two clinical studies, Protocol 010 (refrigerated formulation bridging study) and Protocol 011 (concomitant use study with influenza vaccine) was combined, as well as the safety data from those two studies in the two age groups.

Statistical hypotheses

Success of the trials required satisfying two primary immunogenicity hypotheses:

1. The geometric mean fold rise (GMFR) of VZV antibody responses from prevaccination to 4 weeks postvaccination of ZOSTAVAX among subjects 50 to 59 years of age is noninferior to that among subjects 60 year of age or older.
   (The statistical criterion corresponded to a lower bound of the two-sided 95 % confidence interval [CI] on the GMFR ratio [50 to 59 years of age vs. 60 years of age or older] being >0.67).
2. The GMFR of VZV antibody responses from prevaccination to 4 weeks postvaccination of ZOSTAVAX is acceptable among subjects 50 to 59 years of age and among subjects 60 years of age or older
   (The statistical criterion corresponded to a lower bound of the two-sided 95 % CI of GMFR being >1.4 in each age group.)

The noninferiority margin was identical to that used within the two individual studies for comparisons across vaccination groups. The acceptability lower bound was identical to that used in Protocol 011, but higher than the 1.2 fold rise criterion used in Protocol 010.

Results

Immunogenicity: Noninferiority comparison of VZV antibody response across age groups
Table 1 summarises the VZV antibody responses by age group (50 to 59 years of age; >60 years of age) for the combined studies and for each study individually at day 1 and week 4 postvaccination in the per-protocol population. In each study and in the 2 studies combined, the geometric mean titre (GMT) increased substantially from prevaccination to week 4 postvaccination in both age groups. The overall GMTs for the combined studies at day 1 and week 4 postvaccination were generally comparable between the two age groups. The VZV antibody response, measured by GMFR from prevaccination to week 4 postvaccination, was also generally comparable between the 2 age groups, although numerically slightly higher in the 50 to 59 years of age group, which was consistent across the 2 studies.

Table 1: Summary of VZV gpELISA Antibody Titres Based on Data Combined from Protocol 010 and 011 by Age Group and Study (Per-Protocol Population)

			50 - 59 Years of Age (N=389)		≥60 Years of Age (N=731)	
Protocol	Endpoint	Time Point	n	Observed Responses (95% CI)	n	Observed Responses (95% CI)
010	GMT	Day 1	133	**238.5** (196.0, 290.3)	231	**314.6** (269.9, 366.6)
	GMT	Week 4	128	**747.3** (601.3, 928.6)	226	**797.5** (686.6, 926.4)
	GMFR from Day 1	Week 4	126	**3.2** (2.6, 3.9)	225	**2.5** (2.2, 2.9)
011	GMT	Day 1	252	**269.0** (235.1, 307.7)	494	**255.0** (229.7, 283.1)
	GMT	Week 4	244	**630.2** (558.4, 711.1)	483	**543.1** (496.3, 594.4)
	GMFR from Day 1	Week 4	242	**2.4** (2.1, 2.7)	478	**2.1** (2.0, 2.3)
Combined	GMT	Day 1	385	**258.0** (231.0, 288.3)	725	**272.7** (250.1, 297.3)
	GMT	Week 4	372	**668.2** (599.4, 745.0)	709	**613.9** (567.4, 664.2)
	GMFR from Day 1	Week 4	368	**2.6** (2.4, 2.9)	703	**2.3** (2.1, 2.4)

N = Number of subjects vaccinated.
n = Number of subjects contributing to the immunogenicity summary.

Analysis of Acceptability of VZV Antibody Response

The noninferiority analysis of the VZV antibody response between the age groups was based on the analysis of covariance (ANCOVA) model in which the natural-log-transformed fold rise at week 4 postvaccination was the response variable, and age group, study, vaccination group, and natural-log-transformed prevaccination titres were the covariates. After adjusting for the prevaccination titres, the estimated GMFR ratio (50 to 59 years of age/>60 years of age) was 1.13 (95% CI: 1.02 to 1.25, p= 0.002). Since the lower bound of the 2-sided 95% CI was >0.67 and the one-sided p-value for testing the noninferiority hypothesis was <0.025, the VZV antibody response induced by ZOSTAVAX in subjects 50 to 59 years of age was found to be noninferior to that in subjects >60 years of age. In addition, the fact that the lower bound of the 95% CI of the GMFR ratio was >1 indicates that the GMFR at week 4 postvaccination was slightly higher (reached statistical significance) in subjects 50 to 59 years of age than in subjects >60 years of age.

To further quantify the effect of age, study, vaccination group and the prevaccination titer on the fold rise post vaccination, the results of the ANCOVA model with natural-log-transformed fold rise at week 4 post vaccination as a response variable, and vaccination group, age group, protocol, and log-transformed prevaccination titer as the covariates were provided (see table 2). As observed before, the younger age group (50 to 59 years of age) had a significantly (marginally) higher VZV antibody response at week 4 postvaccination than did the older age group (>60 years of age). A significantly higher VZV antibody response was observed at week 4 postvaccination in Protocol 010 than in Protocol 011.

The level of pre-vaccination VZV antibody titres had a statistically significant (p-value <0.001) effect on the VZV antibody response at week 4 postvaccination. The vaccination group within each study did not have a statistically significant effect on the fold rise at week 4 postvaccination after adjusting for the prevaccination titer.

Table 2: Integrated Statistical Analysis of the Effect of Age Group, Study, Vaccination Group, and Prevaccination Titer on Fold rise from Prevaccination to Week 4 Postvaccination Based on Data Combined From Protocol 010 and Protocol 011 (Per-Protocol Population)

Parameter	Estimated Regression Coefficient (95% CI)†	Fold Difference (95% CI)†
Age group (50 to 59 years versus ≥60 years)	0.119 (0.016, 0.222)	1.13 (1.02, 1.25)
Study (Protocol 010 versus Protocol 011)	0.276 (0.130, 0.422)	1.32 (1.14, 1.53)
Vaccination group (ZOSTAVAX with PGSU versus ZOSTAVAX with PGS)	-0.131 (-0.302, 0.039)	0.88 (0.74, 1.04)
Vaccination group (concomitant versus nonconcomitant)	-0.068 (-0.187, 0.051)	0.93 (0.83, 1.05)
One unit increase in log-transformed pre-vaccination titres	-0.419 (-0.461, -0.377)	0.66 (0.63, 0.69)

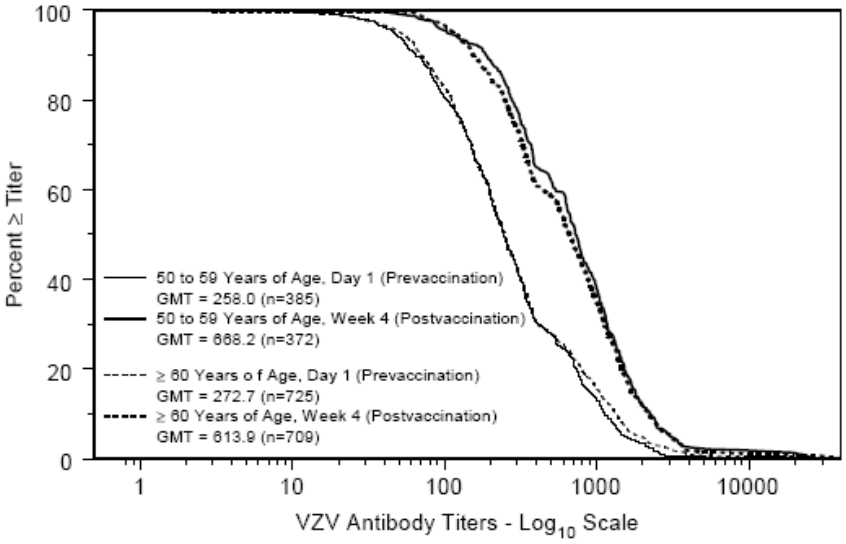
† Computed using an ANCOVA model in which natural-log-transformed week 4 titer was the response variable, and vaccination group, age, and natural-log-transformed prevaccination titres were the covariates.
The p-value for testing the age-group-by-study interaction was 0.867.

As planned in the analysis plan, a test for the age-group-by-study interaction was conducted for the GMFR from prevaccination to week 4 postvaccination. The interaction was not statistically significant (p-value=0.867) at the 10% level, which indicates that the VZV antibody responses at week 4 postvaccination in the 2 age groups were consistent across the 2 studies (Protocol 010 and Protocol 011).

Figure 1 shows the reverse cumulative distribution (RCD) of VZV antibody titres by age group and by visit. Figure 2 displays the RCD of VZV antibody fold rise from prevaccination to week 4 postvaccination by age group in the per-protocol population.
These graphs are consistent with the noninferiority analysis presented in Table 2 and indicate that ZOSTAVAX induced a slightly higher fold rise of VZV antibody response at week 4 postvaccination in the 50 to 59 years of age group than in the >60years of age group.

Figure 1

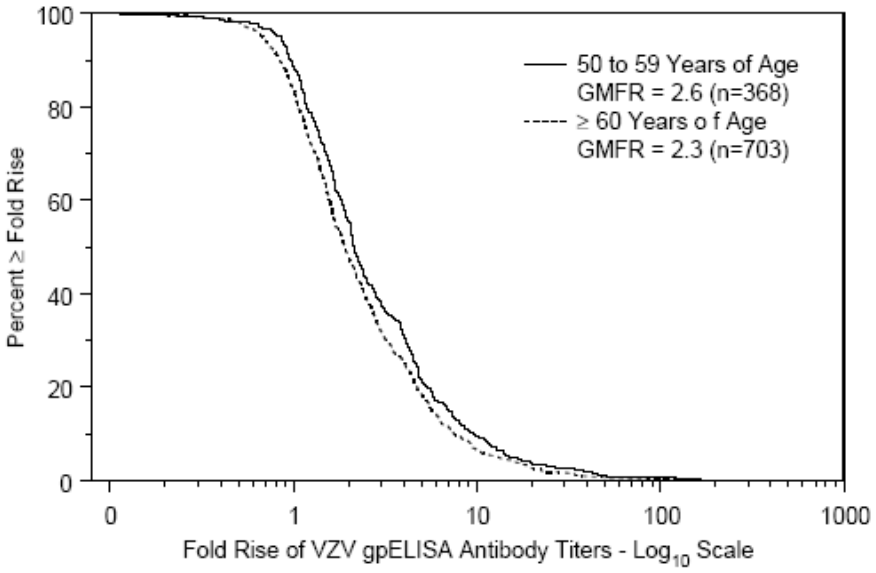
Reverse Cumulative Distribution of VZV gpELISA Antibody Titers Based on Data Combined from Protocol 010 and Protocol 011 by Age Group and Visit (Per-Protocol Population)



n = Number of subjects who had results at the respective time point in each age group.
GMTs are reported in gpELISA units/mL.

Figure 2

Reverse Cumulative Distribution of Fold Rise in VZV gpELISA Antibody Titers Based on Data Combined from Protocol 010 and Protocol 011 From Prevaccination to Week 4 Postvaccination by Age Group
(Per-Protocol Population)



n = Number of subjects who had results at both prevaccination (Day 1) and Week 4 postvaccination in each age group.

The results of the analysis of the GMFR of VZV antibody titres from prevaccination to week 4 postvaccination for both age groups were also provided. The estimated GMFR of the VZV antibody response was 2.6 (95% CI: 2.4 to 2.9) in subjects 50 to 59 years of age and 2.3 (95% CI: 2.1 to 2.4) in subjects >60 years of age. Since each of the lower bounds of the 95% CI was >1.4, and the one-sided p-value for testing the acceptability hypothesis (GMFR >1.4) was <0.025, the criteria for acceptability of the VZV antibody responses induced by ZOSTAVAX in both age groups were met.

Discussion on clinical efficacy

Duration of protection:
The CHMP was concerned, that by vaccinating younger age groups, the outbreak of the disease could possibly be shifted to the older and more vulnerable age groups. Therefore the MAH was requested to commit to carefully follow up this age group and to discuss the need for extension studies in this age group. The MAH was further asked to present a benefit-risk assessment that takes into consideration the effect vaccination at an earlier age would have on the duration of immunity.
In his response, the MAH pointed out that efficacy, immunogenicity and epidemiologic data were available and show the following regarding immune response to varicella-zoster virus (VZV)

- Data from the Shingles Prevention Study (SPS) suggested no waning of protection against HZ through 4 years after vaccination in subjects ≥60 years.
- Vaccine immunogenicity trends provide evidence that the protection against HZ observed in the SPS should extend to individuals 50 to 59 years of age.
- An estimated 300,000 people 50 to 59 years of age develop HZ every year in the EU25; the vast majority of them could be spared the pain and suffering of HZ by vaccination.
- There are no epidemiological data suggesting that developing HZ between 50 and 59 years of age prevents from developing HZ again later in life. In this regard, denial of the benefit of vaccination against HZ for the population 50 to 59 years of age should be weighed against the hypothetical

concern that vaccination beginning at 50 years of age may lead to an increased rate of HZ later in life.

Ongoing follow-up from the long-term extension of the SPS will evaluate the need for a later booster dose in subjects vaccinated ≥60 years at the age, and immunogenicity studies will then be necessary to evaluate the effect of a revaccination. For the age group ≥50 years of age the evaluation of a need for a booster dose will be addressed as committed by the MAH.

The MAH estimated that persons vaccinated between 50 and 59 years of age should have the same or lower level of risk for HZ and PHN when they reach older ages, compared with the risk if they had not been vaccinated. However, it was considered that an assessment of the long-term impact of vaccination on HZ epidemiology would take many years to answer. The MAH therefore committed to undertake an assessment of the feasibility of a postmarketing surveillance system in a country that would implement routine vaccination of individuals 50 to 59 years of age.

The CHMP agreed with the MAH's position that concerns about a potential shift of HZ into a later phase of life (individual risk following early HZ vaccination) or to older age categories (epidemiological effect of routine HZ earlier in life) cannot be taken as a reason for withholding ZOSTAVAX from the group of 50 to 59 years old individuals.

As it was considered that a significant burden of disease exists also in this age category, which can significantly be lowered by vaccination with ZOSTAVAX, concerns as mentioned above were considered secondary. Furthermore, the concept of vaccination to protect from HZ or PHN is new and needs to be followed up with regard to defining optimal revaccination schedules and probably also with regard to numbers of doses needed in individual age categories for efficient immunological stimulation.

The MAH stated that over a period of 4-5 years there was only insignificant waning of the initial immune response in a population vaccinated in the age range of 60 – 69 years (protocol 004). Control over persistence of an effective immune response over a longer period of time will be ensured by protocol 013 which aims at following up individuals vaccinated between 1998 and 2001 until the year 2011. Annual reporting was requested by CHMP at the time of licensing of ZOSTAVAX. Given that follow-up is efficient, i.e. the number of evaluable subjects remains sufficiently high over the observational period it was considered that the understanding of long-term effectiveness of ZOSTAVAX vaccination will become clearer. Since immunogenicity of ZOSTAVAX (as of any other vaccine) is higher in younger compared to older age categories immunological long-term persistence data from protocol 013 are transferable to the 50-59 years old individuals. Nevertheless, the CHMP felt that the MAH should commit to establish age-specific follow-up protocols based on the routine implementation of ZOSTAVAX vaccination in individual (EU)-countries, on which the MAH agreed. Since there is no apparent change in the benefit-risk ratio for the 50-59 old individuals compared to individuals older than 60 years of age at the time of vaccination, the issue was considered solved for the time being.

Impact on epidemiology and need for a booster dose

In the light of the unclear duration of protection, the MAH was also asked to present all available data on the need and timing of a booster dose.

Following the assessment of the responses, the CHMP considered that as discussed in the original application, some of the studies considering two dose schedules demonstrated a further increase of immune responses following a second dose of ZOSTAVAX. The CHMP highlighted that the final immune response did not depend on the titre of the vaccine virus but only on the number of doses given, indicating that moderate but constant exposure to varizella-zoster virus is the best protection against zoster and its sequelae. From that perspective it is agreed that the design of vaccination schedules needs to be refined based on efficient follow-up measures. Protocol 013 is in place to ensure long-term follow up of vaccinated individuals. Again, even if data collected from that protocol might

be extrapolated to younger vaccinated age categories an age specific long-term follow up design is preferred to address the question of defining optimal time points for re-vaccination.

The CHMP agreed with the company that this can best be achieved in parallel to routine implementation of zoster vaccination in individual countries. The MAH committed to keep CHMP updated whenever such vaccination programs start in individual countries and should provide appropriate protocols for efficient follow-up, in particular of the younger vaccinated age groups, which was considered appropriate by the CHMP.

It is known that the incidence of HZ in subjects 50 to 59 years of age is lower than in subjects 60 years and older. Therefore, the CHMP considered that the epidemiology of the disease needs to be closely monitored when vaccinating younger age groups to detect potential shifts of HZ to older ages and more severe outcomes. The MAH was therefore asked to present appropriate measures to detect these potential shifts. Furthermore, the MAH was asked to clarify the impact of vaccination in the younger age group on on-going studies.

The MAH agreed that there is a need to monitor the impact of vaccinating younger age groups on the epidemiology of HZ and proposed Monitoring of HZ epidemiology by large-linked U.S. automated database, such as that at a managed care organization (MCO). In addition, a MCO database was considered to be helpful to monitor the need for hospitalization due to HZ among HZ patients and to determine potential changes of HZ severity over time. However, such a postmarketing observational vaccine effectiveness study in the U.S. would require that ZOSTAVAX be approved in the U.S. for individuals 50 years of age or older, and that routine vaccination is implemented in this age group, at least in the MCO where the study would be conducted. Should these conditions be met in the next few years, the MAH agreed to opt for an effectiveness study to address the issue of long-term impact of HZ vaccination on the epidemiology of HZ. The MAH further committed to provide a preliminary concept sheet for this study to clarify the intended design, structure and organisation of the study.

Additionally, as indicated above, an age-specific long-term follow-up design was supported by the CHMP to address the question of whether wide implementation of a zoster vaccination program for persons greater than 50 years of age would change the age-specific epidemiology of HZ. The CHMP agreed that this can best be achieved in parallel to routine implementation of zoster vaccination in individual countries.

The MAH committed to regularly update the CHMP whenever such a widespread vaccination program is implemented in a country where HZ surveillance would be feasible and will provide a draft protocol for monitoring age-specific HZ epidemiology once routine vaccination of individuals 50 years of age and older is implemented in that country.

Concerning stratification of age groups, the following points were considered important:

- For the younger cohort (50 to 59 years of age), it was expected that if the immunogenicity of ZOSTAVAX is at least equivalent to that in individuals ≥60 years of age, then the reduction in HZ incidence obtained through vaccination will be at least equivalent to that observed in older subjects. This assumption was based on the data from the SPS which show greater immunogenicity and efficacy in subjects 60 to 69 years of age compared with that in subjects ≥70 years of age. In addition, the study data found that higher immune responses were associated with a reduced risk of developing HZ.
- For the older cohort (≥60 years of age), given equivalent immunogenicity in new studies, comparable efficacy was inferred. As demonstrated in the SPS, the administration of ZOSTAVAX in this age group was associated with increased protection against both HZ and PHN.

The CHMP agreed with the position of the MAH that potential changes in the epidemiology of HZ can only be observed once vaccination against HZ has been widely implemented. For the time being, data can therefore only be collected from past clinical studies focused on the long-term follow-up of

vaccinated individuals. In this respect, Protocol 013 will follow up vaccinated individuals until 2011. These individuals were over 60 years of age at the time of vaccination. However, it seems to be highly unlikely that shifts in the epidemiology of HZ can be detected within this study. Potential effects of routine HZ vaccination will require large sample sizes and long-term follow-up periods. Only under these circumstances can age-specific (re-) vaccination protocols be designed in order to assess effectiveness of HZ vaccination accurately.. However, controlled surveillance is only possible once HZ vaccination has routinely been implemented in vaccination programs. This is not the case currently but cannot be taken as a valid reason to withhold ZOSTAVAX from any age category that suffers from significant disease burden due to HZ. Efficacy of ZOSTAVAX against HZ or PHN has unequivocally been demonstrated in the original application for individuals > 60 years of age. Based on immunogenicity results provided with this variation application (protocols 010 and 011) there is currently not a single piece of evidence to believe that efficacy will be different for the 50-59 years old individuals. Thus, the immediate risk-benefit ratio is identical for both age categories. Whether or not this profile will change over time cannot be estimated for the time being. The CHMP reiterated that the MAH is encouraged to submit relevant protocols to CHMP in parallel with routine implementation of ZOSTAVAX vaccination in individual MS following the launch of the product as described above

Impact of gpELISA titres on the risk of developing HZ

As in this variation the immunogenicity was bridged using gpELISA titre data from 4 weeks post vaccination, the CHMP asked the MAH to clarify if gpELISA titres at 4 weeks post vaccination also were associated with a significant reduction in the risk of developing HZ.

Although the SPS did not measure immune responses at 4 weeks post vaccination, the MAH stated that association of 4-week titres with HZ protection could be inferred by the correlation profiles seen in the SPS and the antibody kinetics data in ZOSTAVAX Protocol 007.

Protocol 007 was designed to evaluate the safety and immunogenicity after 1 and 2 doses of ZOSTAVAX in 210 adults, 60 years of age or older. Subjects were randomly assigned to receive 2 doses, 42 days apart, of either ZOSTAVAX or placebo. VZV antibody levels were measured in all subjects by gpELISA at prevaccination and at 2 weeks, 6 weeks, 8 weeks, 12 weeks, and 32 weeks after the first vaccination. Additional time points were tested for subjects enrolled in a Kinetics Substudy.

The VZV antibody GMT and GMFR from baseline at 2 weeks and 6 weeks postvaccination in the ZOSTAVAX group were significantly higher than those in the placebo group. The analyses of GMT ratios at each time point postvaccination (estimated ratio between the ZOSTAVAX group and the placebo group) are presented in Table 3. The GMT ratios were higher at 2 weeks postvaccination compared with 6 weeks postvaccination following any vaccination. Additionally, the observed GMFRs at 2 weeks Postdose 1 and 6 weeks Postdose 1 in the ZOSTAVAX group were 1.9 and 1.6, respectively. The higher responses observed at 2 weeks Postdose 1 suggest that the peak of the immune response occurs earlier than 6 weeks postvaccination. In addition, significant boosting was seen at 2 weeks Postdose 2.

The MAH further responded that in the CMI Substudy of the SPS, the vaccine effect on the reduction of HZ incidence was best correlated with the VZV antibody response at 6 weeks postvaccination measured by gpELISA (titer and foldrise from prevaccination). A Cox regression analysis showed a statistically significant inverse trend for risk of developing HZ with increasing antibody responses by gpELISA at 6 weeks postvaccination ($p<0.001$). Based on this model, each 1 log-unit increase in antibody titer was associated with a significant reduction (38.0%; 95% CI = 20.9, 51.5%; p-value <0.001) in the risk of HZ. Therefore, as the VZV antibody response measured by gpELISA at earlier time points correlates with that at 6 weeks postvaccination, and as the VZV antibody responses measured by gpELISA at 6 weeks postvaccination correlate with the clinical outcome of developing HZ, it was inferred that the VZV antibody response measured by gpELISA at 4 weeks postvaccination also correlates with the vaccine effect. Therefore, the VZV antibody response measured by gpELISA at 4 weeks postvaccination in individuals vaccinated with ZOSTAVAX is an indirect measurement of

the vaccine effect against HZ, and can be used for bridging immunogenicity to efficacy in clinical studies.

The CHMP pointed out that gpELISA values already peak two weeks post dose 1 or 2 indicating that values measured either 4 or 6 weeks post vaccination will equally correlate with the reduction of HZ and considered therefore that the MAH's response was acceptable.

3.3 Clinical safety

Data from previous clinical trials evaluated the safety of the frozen formulation zoster vaccine showed that across these clinical studies, in which more than 20,000 subjects received frozen formulation zoster vaccine, the vaccine was generally well tolerated.

Methods
In Protocol 010 all subjects were followed for safety for 28 days postvaccination. Injection-site reactions, rashes, medications and/or other vaccinations, oral temperatures (if the subject felt feverish), and other adverse experiences were recorded on a VRC. At the end of the 28-day follow-up period (day 29 to 35), study site personnel reviewed all VRCs to ensure that all rashes and adverse experiences were reported. Additionally, at the week 4 visit and at the time subjects were seen for a rash or vaccine-specific illness, site personnel questioned subjects regarding exposure to varicella and/or HZ since vaccination and entered the information on the appropriate Case Report Forms (CRFs).
Subjects were to report immediately to study personnel any episodes of varicella, varicella-like rash, HZ, or HZ-like rash, at any time during the 28-day safety follow-up period, to be seen by the study physician within 72 hours of rash onset, and to undergo physical examination by the study physician until no new lesions appeared and all older lesions were no longer palpable.
Subjects were considered to have completed the study upon returning a completed VRC.

Patient exposure
A total of 367 subjects, 50 years of age and older were vaccinated in Protocol 011. Of these, 182 were randomised to the refrigerated formulation zoster vaccine group and 185 were randomised to the frozen formulation group. The study population included subjects ≥50 years of age in order to provide immunogenicity and safety data in an expanded age group. Enrolment was age-stratified in a 1:2 ratio (50 to 59 years and ≥60 years, respectively).

Results

Table 3 presents an integrated summary of the number and percentage of subjects with clinical adverse experiences reported within 28 days postvaccination, by age group, for subjects vaccinated with ZOSTAVAX in the combined protocols. Safety follow-up was obtained for 1112 of the 1120 vaccinated subjects. In Protocol 010, all vaccinated subjects with safety follow-up where included in the safety summaries and analyses presented in this section. In Protocol 011, only subjects with safety follow-up during the 28-day period following administration of ZOSTAVAX were included. The safety evaluation following administration of placebo and/or influenza vaccine were not included in the following summaries and analyses, except for those subjects who reported systemic clinical adverse experiences following the concomitant administration of influenza vaccine and ZOSTAVAX.

Table 3: Summary of Clinical Adverse Experiences Based on Data Combined from Protocol 10 and Protocol 11 Following Administration of ZOSTAVAX (Days 1 to 28 Postvaccination)

	50 to 59 Years of Age (N=389)		≥60 Years of Age (N=731)	
	n	(%)	n	(%)
Subjects in analysis population	389		731	
Subjects without follow-up	7		1	
Subjects with follow-up	382		730	
Number (%) of subjects:				
with no adverse experience	151	(39.5)	407	(55.8)
with one or more adverse experiences	231	(60.5)	323	(44.2)
Injection-site adverse experiences	193	(50.5)	250	(34.2)
Systemic adverse experiences	96	(25.1)	139	(19.0)
with vaccine-related† adverse experiences	199	(52.1)	256	(35.1)
Injection-site adverse experiences	193	(50.5)	249	(34.1)
Systemic adverse experiences	22	(5.8)	21	(2.9)
with serious adverse experiences	1	(0.3)	5	(0.7)
with serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse experience	0	(0.0)	1	(0.1)
discontinued due to a vaccine-related adverse experience	0	(0.0)	0	(0.0)
discontinued due to a serious adverse experience	0	(0.0)	1	(0.1)
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably, or definitely related to the vaccine.
‡ Discontinued = Subject discontinued from therapy.
Percentages are calculated based on the number of subjects with follow-up.

As shown above 60.5% of subjects 50 to 59 years of age reported one or more clinical adverse experiences, whereas 44.2% of subjects ≥60 years of age reported one or more clinical adverse experiences. In subjects 50 to 59 years of age, approximately 25.1% of subjects reported systemic clinical adverse experiences, but only 5.8% of subjects reported vaccine-related systemic clinical adverse experiences. In subjects ≥60 years of age, 19.0% of subjects reported systemic clinical adverse experiences, but only 2.9% of subjects reported vaccine-related systemic clinical adverse experiences. These results indicate overall a higher rate of adverse events in the lower age group.

Table 4 below displays the estimated risk of developing clinical adverse experiences in each age group stratified by protocol and vaccination group, along with the estimated risk differences between the 2 age groups with their 95% CIs. In general, the two age groups were comparable with respect to reporting serious adverse experience as the corresponding 95% CIs for the risk differences included zero. The risk of reporting systemic and injection-site adverse experiences in subjects 50 to 59 years of age than in subjects >60 years of age reached statistical significance, since the 95% CI for the risk differences excluded zero.

Table 4: Statistical Analysis of Clinical Adverse Experiences Based on Data Combined from Protocol 010 and Protocol 011 Following Administration of ZOSTAVAX (Days 1 to 28 Postvaccination)

	Age Group				Estimated Risk† Difference in Percentage Points (95% CI)
	50 to 59 Years of Age (N=389)		≥60 Years of Age (N=731)		
	n	Estimated Risk (%)	n	Estimated Risk (%)	
Number of subjects vaccinated	389		731		
Subjects with follow-up	382		730		
Subjects without follow-up	7		1		
Number (%) of subjects vaccinated					
with no adverse experience	151	(39.7)	407	(55.8)	
with one or more adverse experiences	231	(60.3)	323	(44.2)	16.1 (10.0, 22.1)
injection-site adverse experiences	193	(50.4)	250	(34.2)	16.1 (10.0, 22.2)
systemic adverse experiences	96	(25.1)	139	(19.0)	6.1 (1.0, 11.4)
with vaccine-related‡ adverse experiences	199	(51.9)	256	(35.1)	16.9 (10.8, 22.9)
injection-site adverse experiences	193	(50.4)	249	(34.1)	16.3 (10.2, 22.3)
systemic adverse experiences	22	(5.7)	21	(2.9)	2.8 (0.4, 5.8)
with serious adverse experiences	1	(0.3)	5	(0.7)	-0.4 (-1.4, 0.9)
with serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)	0.0 (-0.5, 1.0)
who died	0	(0.0)	0	(0.0)	N/A
discontinued§ due to an adverse experience	0	(0.0)	1	(0.1)	-0.1 (-0.8, 0.9)
discontinued due to a vaccine-related adverse experience	0	(0.0)	0	(0.0)	N/A
discontinued due to a serious adverse experience	0	(0.0)	1	(0.1)	-0.1 (-0.8, 0.9)
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)	N/A

N = Number of subjects vaccinated.
n = Number of subjects reporting adverse experiences in the respective category.

The adverse experience logs of both studies 010 and 011 regarding the severity confirm that the majority of the experiences were mild and moderate in both age groups.

One (0.3%) out of 382 subjects with safety follow-up and 5 (0.7%) out of 730 subjects with safety follow-up reported serious clinical adverse experiences in the 50 to 59 years of age group and the >60 years of group, respectively. These events were convulsion, gastroenteritis, basal cell carcinoma, cardiac failure congestive, aortic valve stenosis, arrhythmia, myocardial infarction, acute pulmonary oedema, chronic obstructive pulmonary disease, pneumonia, respiratory failure and upper limb fracture. No ZOSTAVAX related serious clinical adverse experience was reported in the two studies. This provides 97.5% confidence that the true vaccine related serious adverse experience rate was <0.96% (1 out of every 104 subjects) in 50 to 59 years of age. Furthermore, no deaths occurred during

the conduct of either study. One (1) subject >60 years of age discontinued due to a serious clinical adverse experience in Protocol 011.

The MAH presented also a summary of the number and percentage of subjects with specific systemic clinical adverse experiences (incidence ≥1% in one or both age groups), by system organ class and age group, days 1 to 28 postvaccination for the combined clinical studies.
Approximately 25% of the subjects 50 to 59 years of age and 19% of the subjects >60 years of age reported at least one systemic clinical adverse experience. The most commonly reported systemic clinical adverse experiences in subjects 50 to 59 years of age were headache (4.5%), upper respiratory tract infection (2.9%), and back pain (2.1%). Among these most commonly reported systemic clinical adverse experiences, 1.0% of the headaches were deemed to be vaccine-related. The most commonly reported systemic clinical adverse experience in subjects >60 years of age was upper respiratory tract infection (2.1%) and 0.3% of these were deemed to be vaccine-related. Overall, the number and percentage of subjects reporting any systemic clinical adverse experiences were greater in the younger age group than in the older age group.

Discussion on clinical safety

Safety in the 50 to 59 year age group
The CHMP noted that the number and percentage of subjects reporting any systemic clinical adverse experience were greater in the 50 to 59 year group as compared to the > 60 year group. The CHMP further noted, that the AEs from the SOC Nervous System Disorder were 5.5% in the younger age group while 1.5% in the older age group although 1.6% were determined vaccine related in the younger group and 1.1% in the older group. The CHMP considered that the nature of neurological AEs other than headache should be clarified, especially regarding serious AEs. Since vaccine reactogenicity was higher in the 50-59 year group, the CHMP requested that safety follow-up including rare serious adverse events should be monitored during widespread use.

The MAH clarified in his response the nature of the remaining nervous system adverse experiences, in addition to headache. Convulsion (n=1 in the 50-to-59 stratum), dizziness (n=1 in the 50-to-59 stratum and n=3 in the 60-and-older stratum), and lethargy (n=1 in the 50-to-59 stratum) were the other nervous system adverse experiences reported. Of these, only the case of convulsion was considered by the investigator to be a serious clinical adverse experience. However, it was not considered to be vaccine-related and was determined that it was induced by fatigue.

The overall incidence of adverse experiences from the Nervous System organ class (SOC) was statistically higher in the younger age group than in the older age group, with headache reported at a significantly higher frequency by subjects 50 to 59 years of age than by subjects ≥60 years of age. These adverse experiences were not limited to one type of adverse experience and the numbers of reported experiences were still quite low. In addition, the risk of reporting systemic clinical adverse experiences was slightly higher in subjects 50 to 59 years of age than in subjects ≥60 years of age, across almost all SOCs. No other specific adverse event stands out as being more common with decreasing age.

Therefore, only the difference in risk of headache was significantly higher among subjects 50 to 59 years of age than in subjects ≥60 years of age. It should be noted that headache was reported as mild or moderate in intensity in most cases and no other significant age-related trends were observed.

The MAH agreed that the assessment of safety in individuals 50 to 59 years of age, including observation for rare serious adverse experiences, should continue post marketing. The post marketing setting will permit a better monitoring for rare adverse experiences at a level that is not achievable through clinical trials and committed to monitor serious AEs stratified by age in the next PSURs

The CHMP considered that a more detailed analysis of the SOC “nervous system disorders” as provided by the MAH would not support any evidence for increased neurological disorders in the 50-

59 years old vaccinated individuals compared to over 60 years old individuals. The spectrum of reported disorders is broad and unspecific and correlation to vaccination not possible, therefore the CHMP considered the issue resolved.

3.4 Risk Management plan

The MAH included an updated Risk Management Plan (RMP) in the application, which has been adapted to the expanded age group of individuals from 50 years of age and older. The MAH presented the safety concerns together with the respective pharmacovigilance activities and proposed risk minimisation activities as outlined in the table below.

Table 5: Summary of the risk management plan for ZOSTAVAX®

Safety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
1- Herpes Zoster-like or Varicella-like Rashes temporally associated with Zoster Vaccine	1. Routine Pharmacovigilance activities 2. Reports of adverse experiences involving HZ-like or varicella-like rashes may be received in the postmarketing period. Although these events may be temporally associated with the administration of ZOSTAVAX, it is also possible that these events may be related to wild-type VZV or may not be related to VZV at all. It is not possible to distinguish clinically or serologically whether these rash illnesses are related to the presence of Oka/Merck vaccine virus or to the wild-type virus. In order to help resolve these issues, it is proposed that health care providers reporting these adverse experiences be offered the opportunity to submit specimens to the Varicella Zoster Virus Identification Programme (VZVIP)	Addressed in the SPC in sections 4.8 and 5.1 PCR analysis through VZVIP
2- Potential transmission of Oka/Merck Vaccine Virus Strain	1. Routine Pharmacovigilance activities 2. In order to help resolve these issues, it is proposed that health care providers reporting these adverse experiences be offered the opportunity to submit specimens to the VZVIP.	Warning in section 4.4 of the SPC PCR analysis through VZVIP
3- Exposure of Immunocompromised Individuals	1. Routine Pharmacovigilance activities 2. Planned safety and immunogenicity clinical studies	Addressed in the SPC in sections 4.3, 4.4 and 5.1
4- Potential Central Nervous System Events	1. Routine Pharmacovigilance activities 2. In order to help resolve these issues, it is proposed that health care providers reporting these adverse experiences be offered the opportunity to submit specimens to the VZVIP including cerebrospinal fluid analyzed by PCR.	PCR analysis through VZVIP
5- Potential for Allergic Reactions	1. Routine Pharmacovigilance activities 2. Warnings regarding adverse events and the contra indication for specific populations through product labelling.	Warning in section 4.4 of the SPC

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
6- Duration of Protection and Need for Booster Dose	Completing a long-term persistence study of efficacy among subjects who received the vaccine during the efficacy trial, Protocol 004	
7- Concomitant Administration with Other Vaccines	A study is planned to evaluate the concomitant use with other adult vaccines	Addressed in the SPC in section 4.5
8- Exposure to ZOSTAVAX® during pregnancy	1. Routine Pharmacovigilance activities 2. The pregnancy registry for VARIVAX will be expanded to include all VZV vaccines, including ZOSTAVAX	Contraindication in section 4.3 of the SPC Addressed in the SPC in sections 4.4 and 4.6 Pregnancy registry
9- Detection of Unanticipated Safety Signals	1. Routine Pharmacovigilance activities 2. Three studies as part of a regulatory commitment: - Post marketing, placebo-controlled general safety study - Large-scale (20 000 vaccinated subjects) observational post licensure safety study - Clinical trial to assess long-term duration of protection among subjects who received the vaccine during the efficacy trial, Protocol 004	

One of the safety concerns presented in the RMP was the duration of protection afforded by vaccination with ZOSTAVAX, which is unknown at present. The initial application for licensure included follow-up for up to 4 years postvaccination for efficacy. The need for a booster dose, if any, is not known.

Concerns have been raised regarding the possibility that immunisation with ZOSTAVAX may delay the onset of HZ if the duration of protection from a single dose is insufficient, therefore possibly shifting the occurrence of HZ to an older age. The MAH committed to completing a long-term persistence study of efficacy among subjects who received the vaccine during the efficacy trial, Protocol 004. Extension of follow-up of approximately 7000 vaccine recipients and approximately 6900 placebo recipients in Protocol 004 is ongoing and was initiated in 2004. By design, this amendment allows for collection of persistence of efficacy data through 4 to 6 years postvaccination.

In order to study longer-term persistence of efficacy, the MAH is currently conducting Protocol 013 (with an anticipated number of N~7000 participants), which extends follow-up of these vaccine recipients through approximately 10 years postvaccination. These subjects were vaccinated in 1998 to 2001 and if waning of protection occurs, it will be detected in this study population before vaccine efficacy is expected to wane in the general vaccinated public. Based on the observations in Protocol 005, should vaccine efficacy wane in later years postvaccination, subsequent doses of vaccine would be expected to boost VZV-specific immunity.

Therefore, Annex II has been updated accordingly to reflect the latest version of the RMP.

3.5 Overall Discussion and Benefit/Risk Assessment

Immunogenicity of ZOSTAVAX observed in studies 010 and 011 (as measured by gpELISA units in the individual and integrated analyses) was within the range observed in previous studies, which were previously assessed.

There was a slight difference in GMTs and GMFRs before and after vaccination between the different age groups receiving ZOSTAVAX. The GMTs and GMFRs were higher in the age group 50 to 59 years of age in comparison to the age group > 60 years of age which was expected since already previously observed. Finally, all pre-defined statistical criteria were met for immunogenicity analyses regarding the age groups below and above 60 years.

The CHMP could not identify any individual or collective risk linked to the extension of the age indication of ZOSTAVAX for individuals from 50 years of age onwards. Furthermore, the favourable risk-benefit ratio identified in the original Marketing Authorisation application for over 60 years old individuals remains unchanged. This can be also extended to the younger age category as supported by studies 010 and 011. The CHMP further concluded that there is currently no ideal tool to investigate immediate and long-term effects that HZ vaccination might have on the general population. Protocol 013 describing the long-term follow-up of individuals over 60 years of age at the time of vaccination was considered unsuitable to fully address the initial concerns regarding the younger population. These concerns can only be addressed specifically once HZ vaccination has been implemented into national vaccination schedules, which is currently not the case.
For the time being concerns discussed above do not justify to withhold vaccination against HZ from the group of 50 – 59 years old individuals which in total suffers from a significant burden of disease caused by HZ. From this perspective, variation on the extension of age range was considered approvable as the MAH committed to provide appropriate study plans in time to measure effects prompted by routine HZ vaccination once ZOSTAVAX is implemented for routine vaccination in a given country.

No safety signals that could give rise to a concern have been detected for any of the age categories, which were investigated in the two groups of study 010 and 011 receiving ZOSTAVAX. A slightly higher proportion of subjects reporting overall systemic and injection-site adverse experiences is observed in the age group 50 to 59 years of age than in subjects > 60 years of age. Although the CHMP considered that this finding could not be translated in a true clinical concern for most of the events, the CHMP pointed out that the adverse events related to the System Organ Class (SOC) “nervous system disorder” were higher in the younger age group than in the older age group. The CHMP considered that the nature of these events were sufficiently clarified by the MAH. However, the MAH agreed with the CHMP that rare serious adverse events will be monitored in the next PSURs, startified by age group.
Systemic clinical adverse events seen in the younger age category were not serious in general (most commonly headache, symptoms of upper respiratory infection, back pain) and were not considered clinically significant by the CHMP.